Vedolizumab

Takeda Pharmaceuticals USA, Inc.

Joint GIDAC and DSaRM Meeting

December 9, 2013

Vedolizumab

Colleen Costello, PhD

Senior Director Regulatory

Takeda Pharmaceuticals International Co.

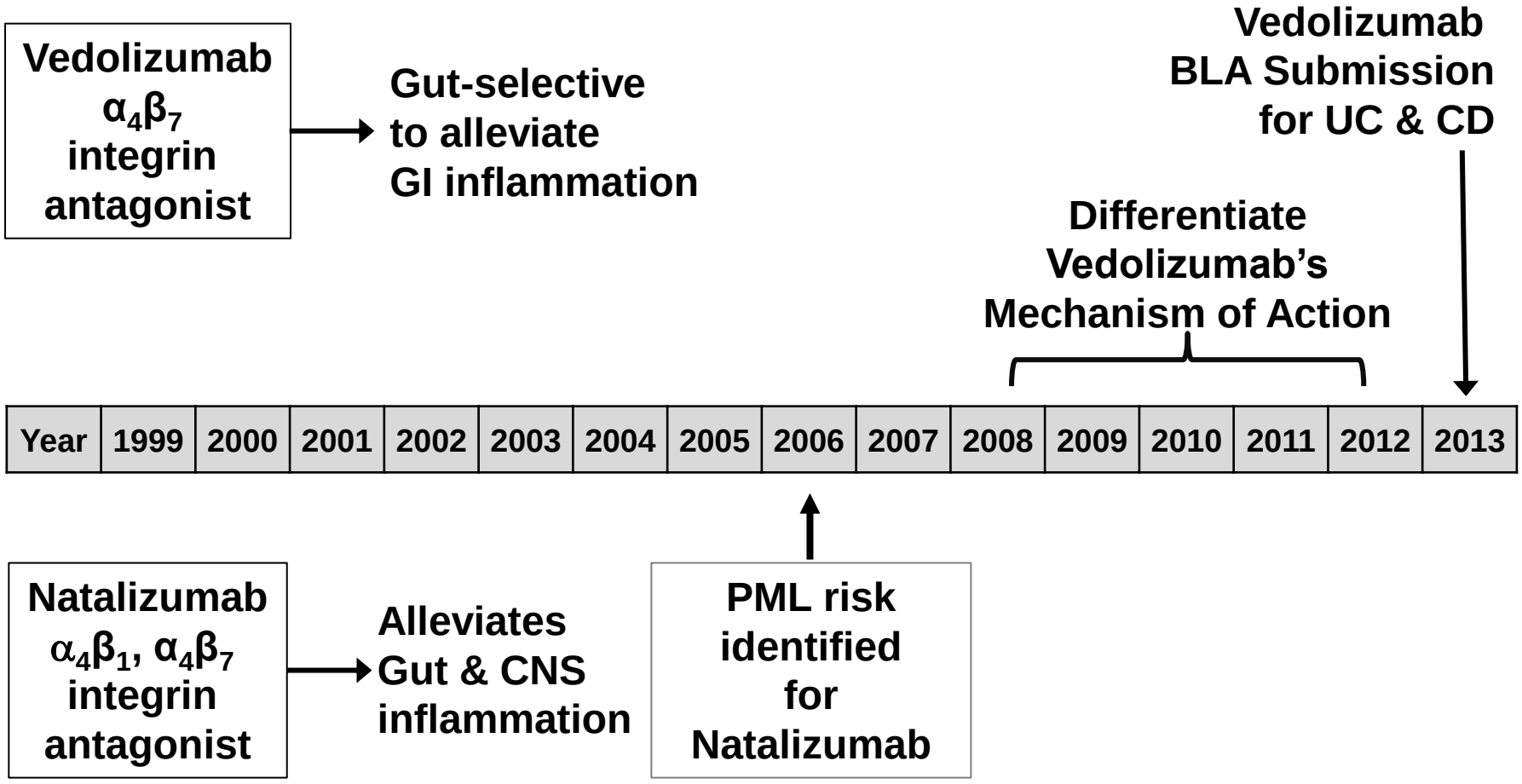
Similar Proposed Indications for Ulcerative Colitis & Crohn's Disease

- Reducing signs and symptoms of disease
- Inducing and maintaining clinical response and clinical remission
- Reducing corticosteroid use
- Inducing and maintaining mucosal healing (UC only)
- In patients
  - With moderate to severely active UC or CD
  - Who were intolerant of, or had inadequate, or lost response to at least 1 conventional therapy or TNFα antagonists

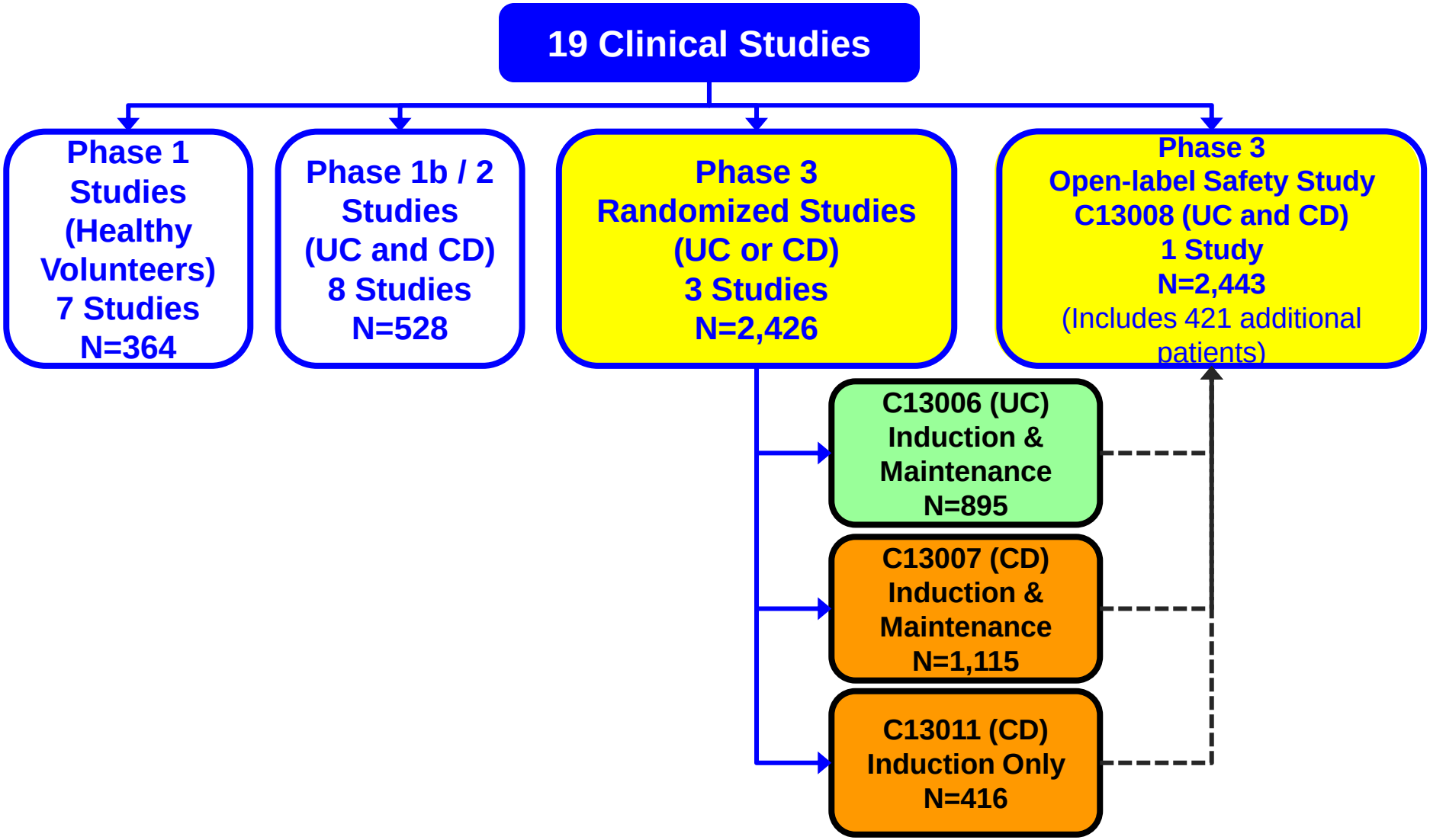
Vedolizumab is Dosed as Fixed 300mg IV Infusion

- Administered at Week 0, Week 2, and Week 6
- Then every 8 Weeks (Q8w) for Maintenance therapy

Vedolizumab Mechanism is Distinct From Other Approved Integrin Antagonists



Vedolizumab Development Program: 19 Clinical Studies Since 1998



US Patients Met All Criteria of the Global Protocol

- Phase 3 clinical trials conducted in 39 countries
- FDA required a US-specific amendment to all protocols
  - Restrict patient eligibility: no primary corticosteroid failures
  - Restrict use of concomitant medications

Vedolizumab Clinical Experience in 3,129 Patients with UC or CD (Data cut 6/27/13)

Months Exposure	Ulcerative Colitis (n=1,279)	Crohn's Disease (n=1,850)	UC + CD Combined (N=3,129)
≥ 12 months	588	830	1,418
≥ 24 months	428	478	906
≥ 36 months	198	209	407

- >1,000 UC and CD patients exposed to ≥ 24 infusions, plus 4 weeks follow-up
- Approximately 1,100 patients in ongoing long-term study*
- No cases of PML*

*** As of December 1, 2013**

Vedolizumab Agenda

Unmet Need in UC and CD	**Bruce Sands, MD** Dr. Burrill B. Crohn Professor of Medicine Chief, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai Hospital, New York, New York
Scientific Rationale for Vedolizumab Development	**Ulrich von Andrian, MD** Mallinckrodt Professor of Immunopathology Division of Immunology, Harvard Medical School, Boston, Massachusetts
Efficacy and Safety: UC and CD	**Asit Parikh, MD, PhD** VP, Gastroenterology and General Medicines Takeda Pharmaceuticals International, Inc.
Differentiation of Vedolizumab	**Joseph Berger, MD** Ruth L. Works Professor, Director of the MS Center University of Kentucky College of Medicine Lexington, Kentucky
Risk Management Plan	**Lesley Wise, PhD** VP, Global Pharmacovigilance Risk Management and Pharmacoepidemiology, Takeda Development Centre Europe, Ltd.
Clinical Perspective	**Bruce Sands, MD** Dr. Burrill B. Crohn Professor of Medicine Chief, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai Hospital, New York, New York

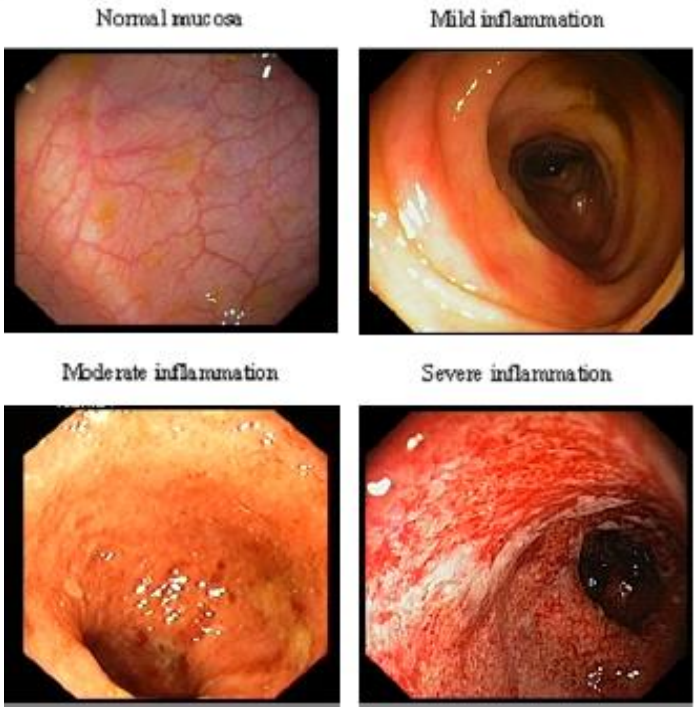
Vedolizumab: Additional Experts

David Clifford, MD	Professor of Neurology Washington University School of Medicine St. Louis, MO Head of Vedolizumab Independent Adjudication Committee for PML
Brian Feagan, MD	Professor of Medicine, Epidemiology and Biostatistics University of Western Ontario, Canada Head of Vedolizumab Steering Committee
Judith Jones, MD, PhD	President & CEO The Degge Group, Ltd. Arlington, VA
Nan Laird, PhD	Harvey V. Fineberg Professor of Public Health, and Professor of Biostatistics Harvard School of Public Health Boston, MA

Unmet Need and Standard of Care in Ulcerative Colitis and Crohn's Disease

Bruce Sands, MD
Dr. Burrill B. Crohn Professor of Medicine
Chief, Division of Gastroenterology
Icahn School of Medicine at Mount Sinai
Mount Sinai Medical Center
New York, NY

Ulcerative Colitis is Characterized by Inflammation of the Colon



Symptoms

- Bloody diarrhea
- Abdominal pain
- Weight loss
- Fever
- Incontinence

Complications

- Colon perforation and toxic megacolon in fulminant cases
- Increased colon cancer risk

de Lange, BMC Gastroenterology (2004)

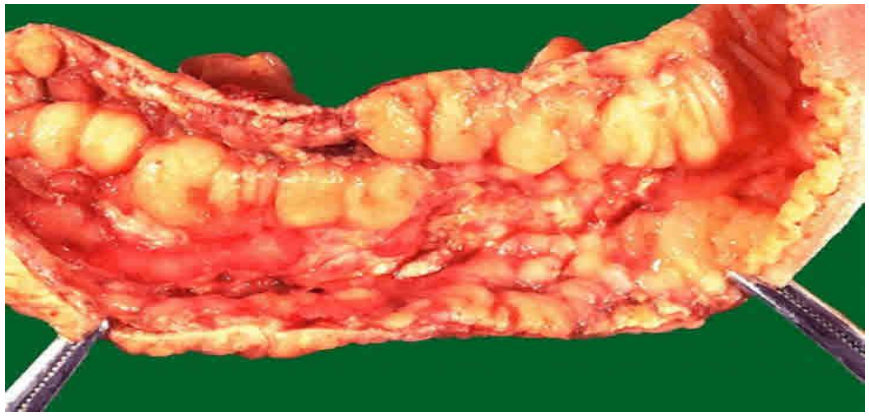
Crohn's Disease is Characterized by Inflammation of the GI Tract

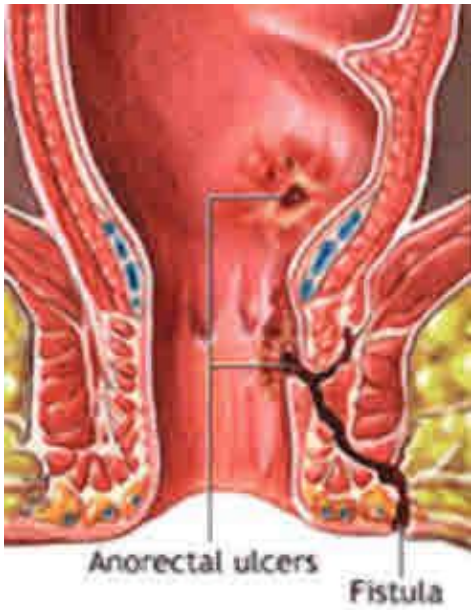
Symptoms

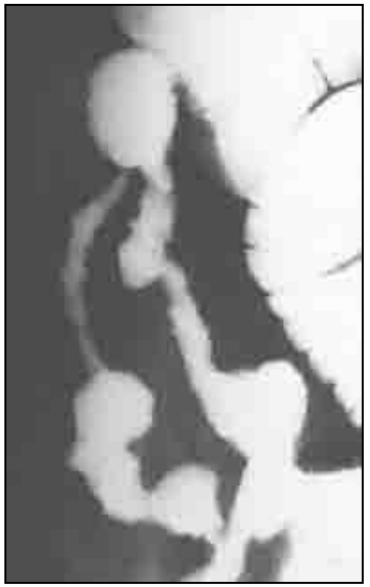
- Diarrhea
- Abdominal pain
- Weight loss
- Fever
- Bleeding

Complications

- Stricture
- Bowel obstruction
- Perforation
- Fistulae
- Increased cancer risk







de Lange, BMC Gastroenterology (2004)

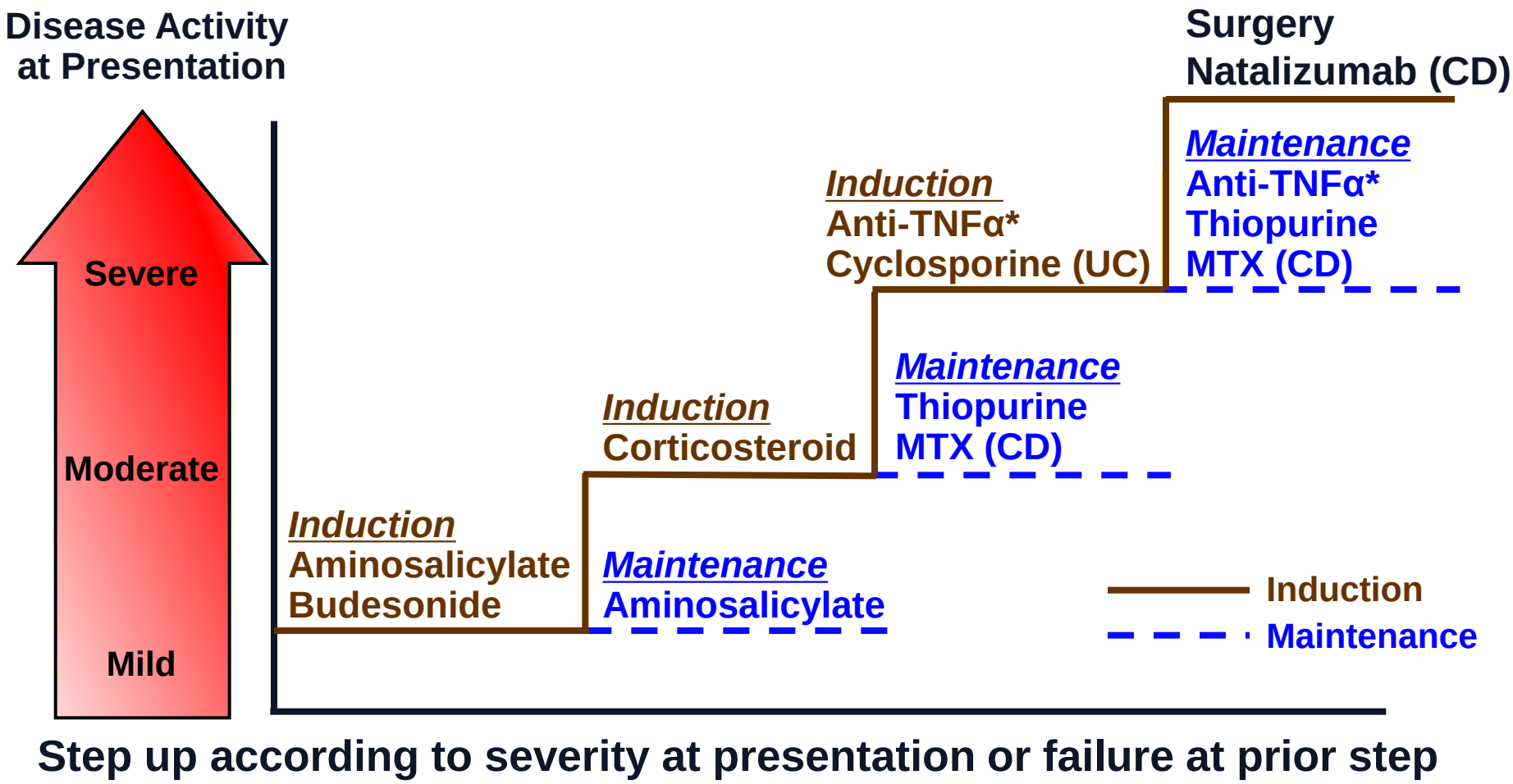
"Disease Activity" is Not Synonymous With Disease Severity

- Disease activity reflects level of symptoms/inflammation at the time measured

	Disease Activity	Scores: Moderately to Severely Active Disease
Ulcerative Colitis	**Mayo Score**	**6 - 12**
Crohn's Disease	**Crohn's Disease Activity Index (CDAI)**	**220 - 450**

- Disease severity reflects long-term course and response to therapy

Treatment Paradigm for IBD is Based on Limited Therapeutic Choices



* Treatment may cycle through multiple agents

Anti-TNFα Antibodies Are Effective But Have Diminishing Durable Response

- ~1/3 do not respond to induction
  - ~20% lose response each year
  - <30% have durable remission at 1 year
- SAE risk for lymphoma, lupus-like reactions, skin lesions, demyelinating disorders, CHF, infections
- Anti-TNFα is last line of treatment
  - Surgery is remaining option

Increasing Patient Disease Severity in Studies of Biological IBD Drugs

	Treatment of Moderately-to-Severely Active Crohn's Disease				
	Infliximab TARGAN[1]	Adalimumab CLASSIC 1[2]	Natalizumab ENCORE[3]	Certolizumab PRECISE 1[4]	Vedolizumab GEMINI II[5]
Year Published	1997	2006	2007	2007	2012
Median Baseline CDAI	288-312	301	303	300	327
Mean Disease Duration (Years)	10-12	n.a.	10	7	9
% Prior Surgery for CD	40-50%	n.a.	n.a.	36%	45%
% Prior TNFα use	0	0	50%	30%	50%
% TNFα Failure	0	0	n.a.	n.a.	48%
% 2-3 TNFα Failures	0	0	n.a.	0	26%
Induction Remission Effect Size	25-44	24	10	5	8

1.Targan, NEJM (1997); 2. Hanauer, Gastroenterology (2006); 3. Targan, Gastroenterology (2007);
4. Sandborn, NEJM (2007); 5. Sandborn, NEJM. (2013)

n.a. = data not available

Patients Actively Participate in Therapeutic Choices

- Patients seek to manage symptoms so they can work and socialize
  - Few remaining treatment options
- Patients have benefit-risk experience with immunomodulators and anti-TNFα antibodies
- Patients with hard-to-treat moderately-to-severely active disease treated by experienced physicians

Need for Unique Treatment Options that Address UC and CD

- Novel MoA
  - Alternative for treatment failures (CS, immunomodulators and/or anti-TNFα)
- Maintain long-term clinical remission or clinical response
- Help stop corticosteroid use
- Integrate into current UC and CD standard of care

A Therapeutic Strategy for Specifically Targeting Gut-homing Leukocytes

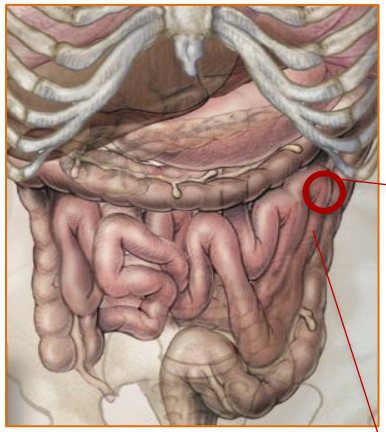
Ulrich von Andrian, MD

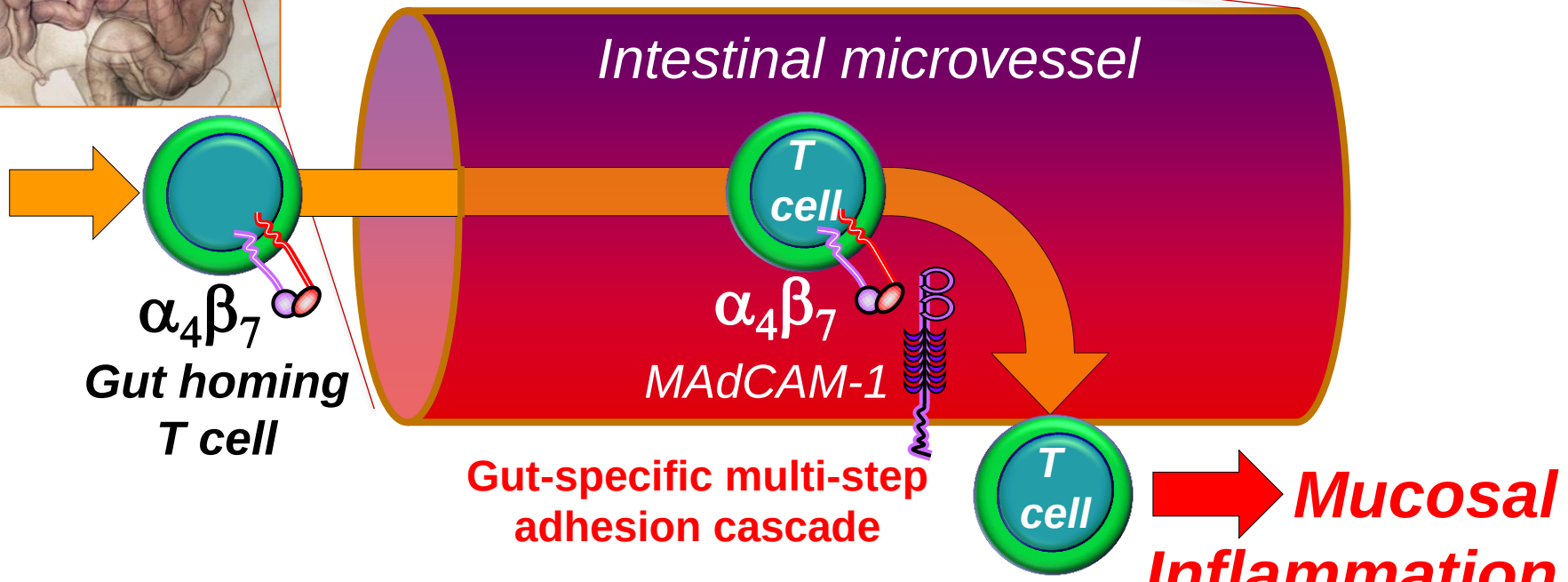
Mallinckrodt Professor of Immunopathology

Harvard Medical School

Leukocyte Extravasation Drives Inflammatory Bowel Disease (UC & CD)

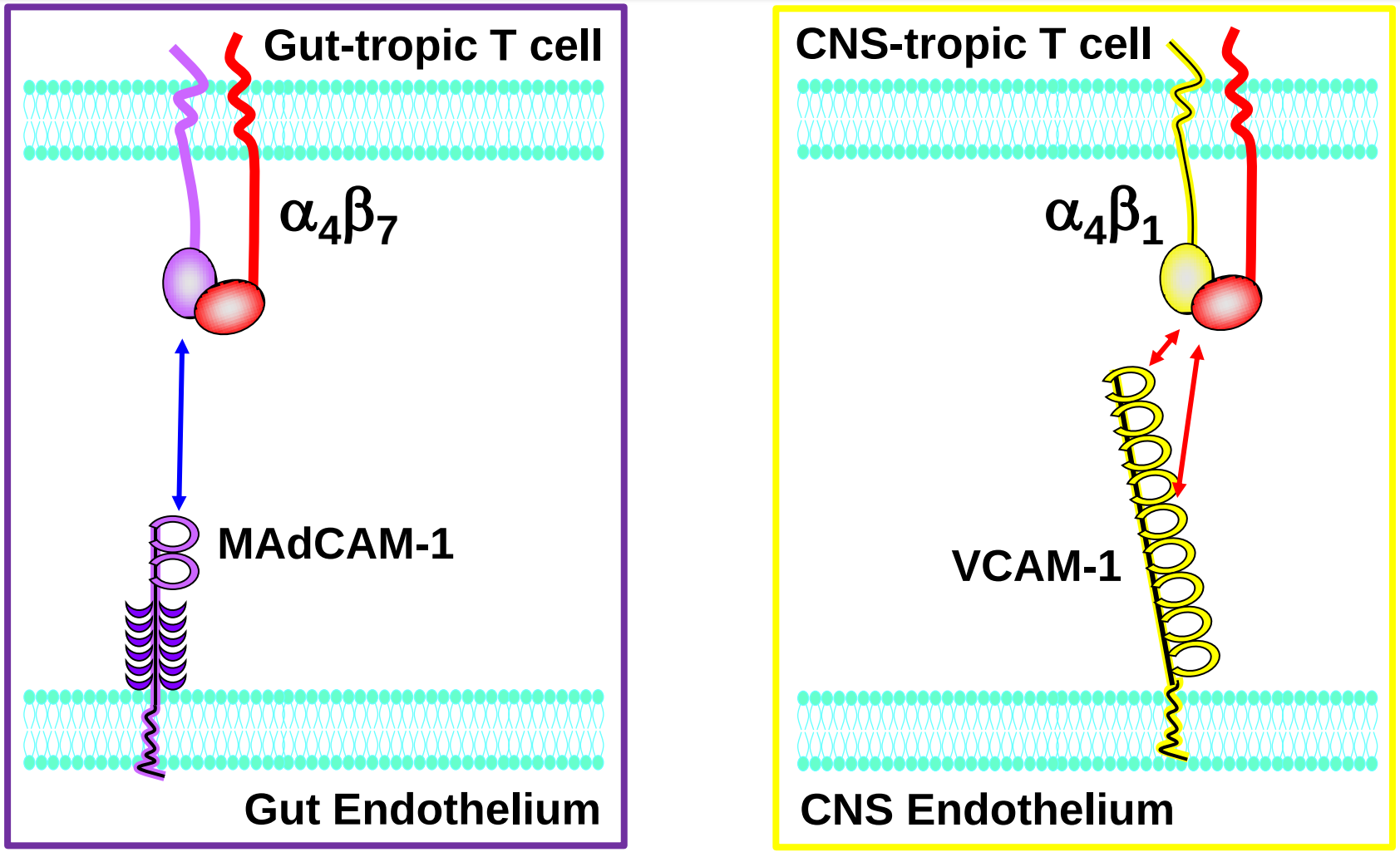
GI Inflammation





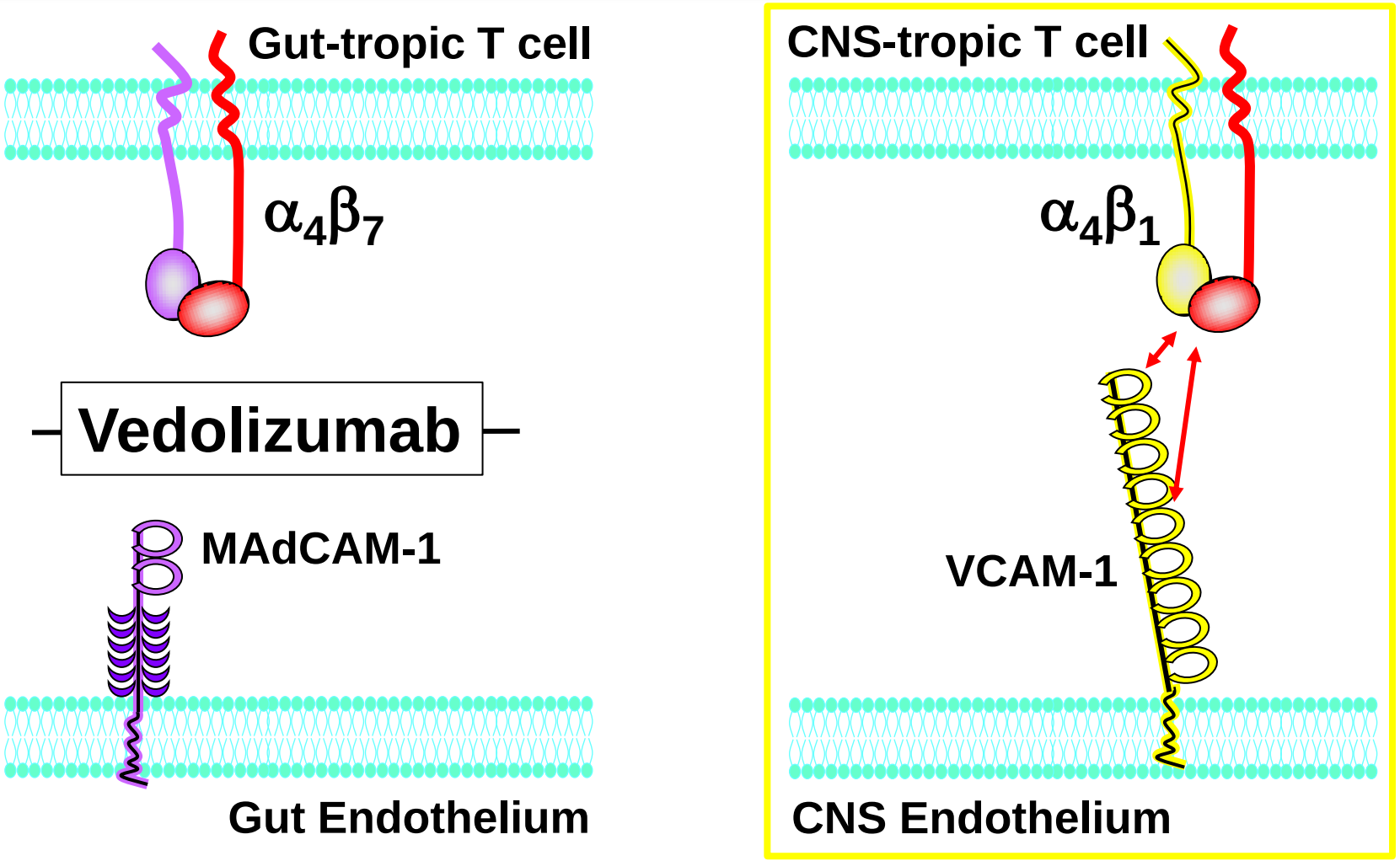
von Andrian & Mackay, *NEJM* (2000)
von Andrian & Engelhardt, *NEJM* (2003)

α4 Integrins and Their Ligands Direct Tissue-tropic Lymphocyte Migration



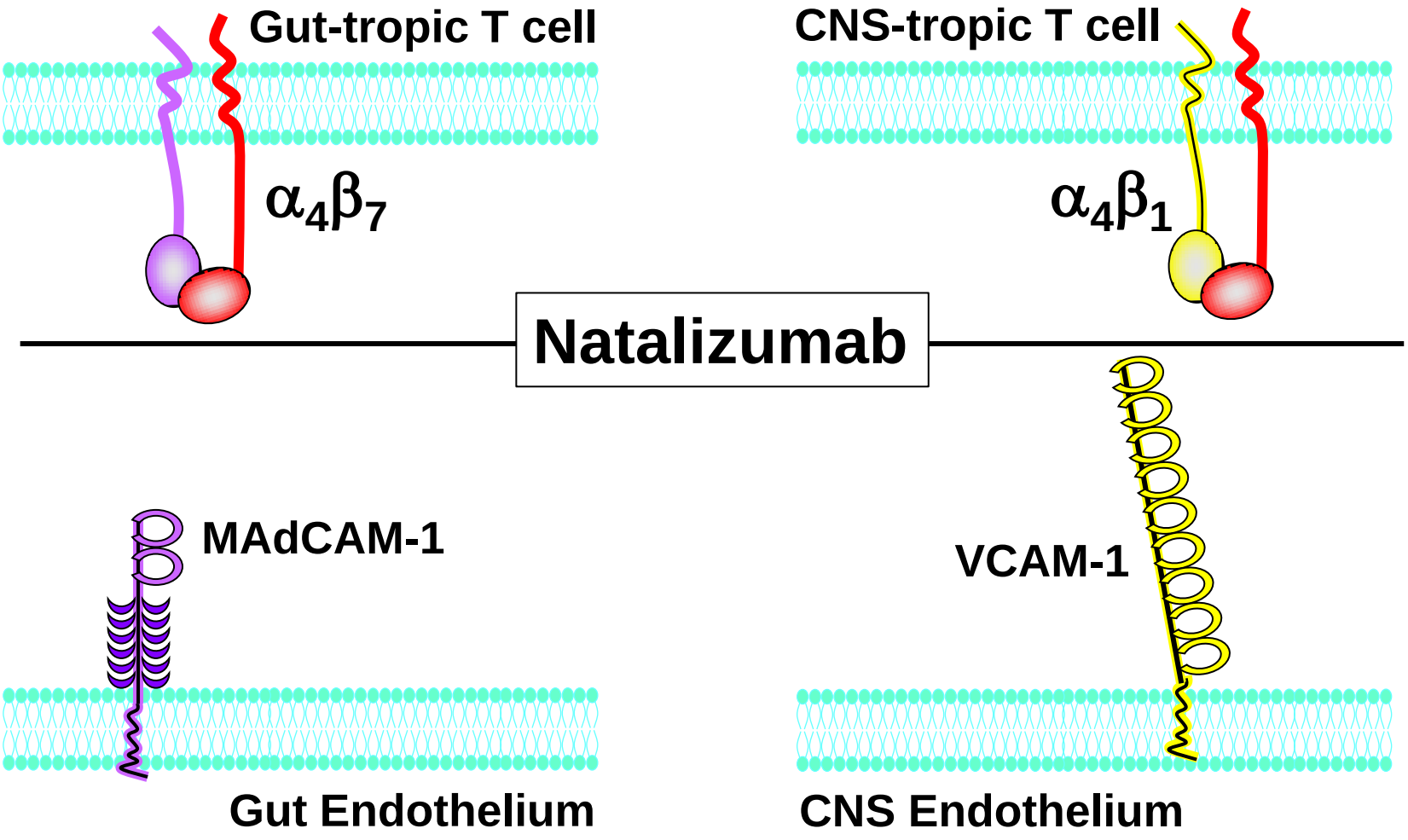
von Andrian & Mackay, *NEJM* (2000); von Andrian & Engelhardt, *NEJM* (2003)

Vedolizumab Specifically Targets Gut-tropic Lymphocyte Migration



von Andrian & Mackay, *NEJM* (2000); von Andrian & Engelhardt, *NEJM* (2003)

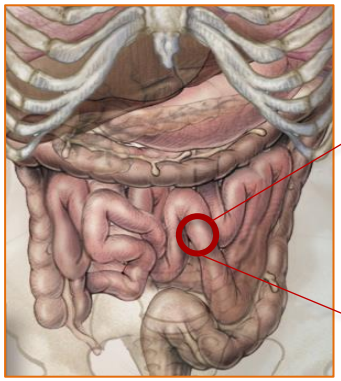
Natalizumab Blocks CNS- and Gut-tropic Lymphocyte Migration



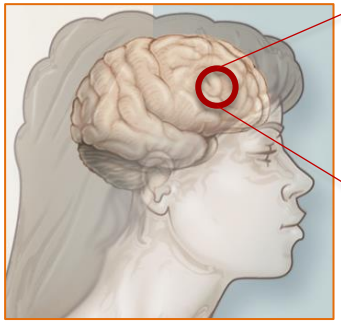
von Andrian & Mackay, *NEJM* (2000); von Andrian & Engelhardt, *NEJM* (2003)

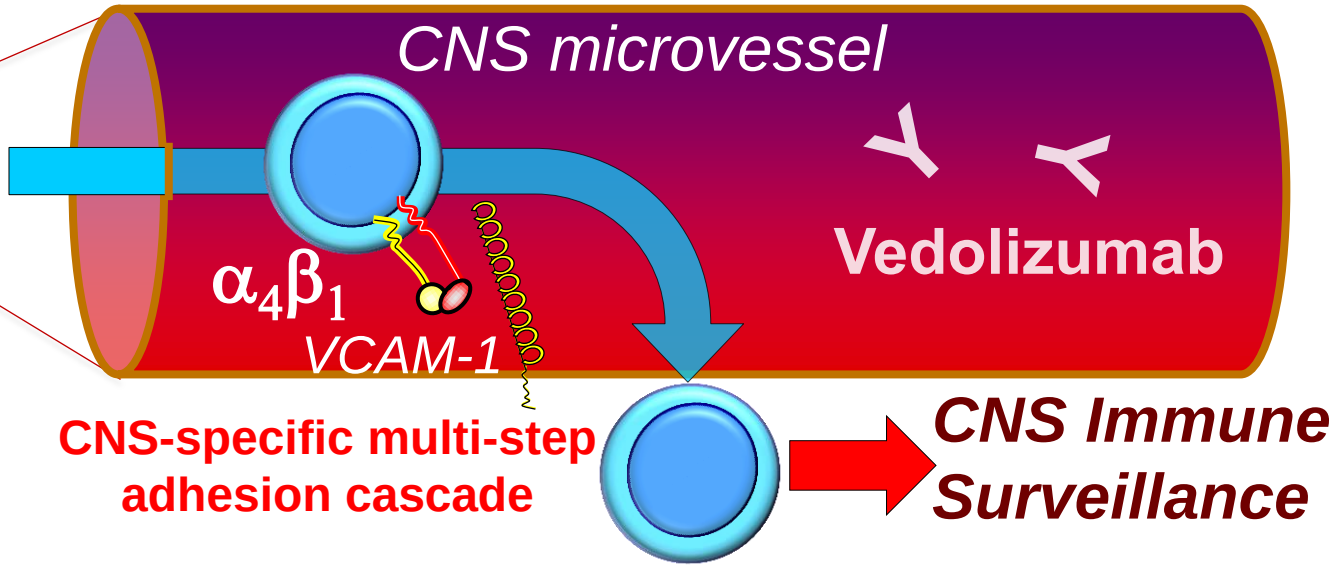
Specifically Targeting the $\alpha_4\beta_7$ Integrin Exerts Gut-selective Effects (UC & CD)

GI Inflammation



CNS Surveillance





von Andrian & Mackay, *NEJM* (2000)
von Andrian & Engelhardt, *NEJM* (2003)
Haanstra *J Immunol* (2013)

Vedolizumab Efficacy
1. Ulcerative Colitis
2. Crohn's Disease

Asit Parikh, MD PhD

VP, Gastroenterology and General Medicines

Takeda Pharmaceuticals International, Inc.

Efficacy Overview

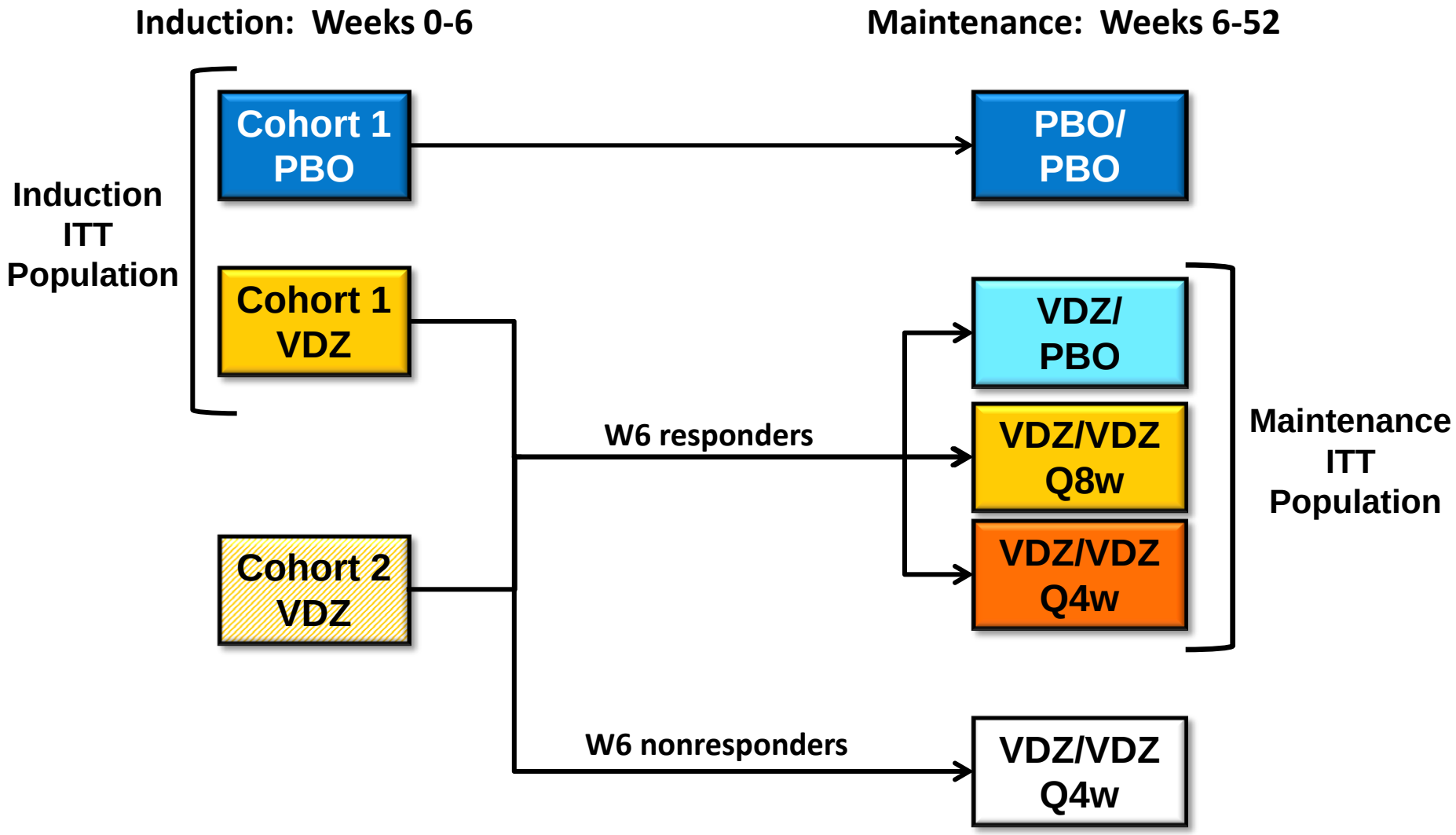
- Clinical Trial Design
- Clinical Results
  - Ulcerative Colitis
  - Crohn’s Disease

Pivotal UC and CD Trials Followed Identical Design

1. Induction Study
   - Randomization to VDZ vs placebo
   - Week 6 endpoint
2. Maintenance Study
   - VDZ induction responders randomized to VDZ or placebo
   - Week 52 endpoint

➢ Endpoints of 2 studies powered separately

Phase 3 Trials: Two Independent Studies – Induction and Maintenance



Ulcerative Colitis Efficacy

Study C13006

Induction

Maintenance

UC (C13006): Phase 3 Study Enrolled Moderately-to-Severely Active Patients

Criterion	C13006 (UC)
Disease Duration	≥ 6 months
Localization	≥ 15 cm colon
Disease Activity	Mayo score 6–12 Active flare: Mayo endoscopic sub-score ≥ 2
Prior Medication Failure	Anti-TNFα Immunomodulators (AZA, 6-MP, MTX) Corticosteroids (ex-US)

UC (C13006): Efficacy Endpoints for Induction and Maintenance Studies

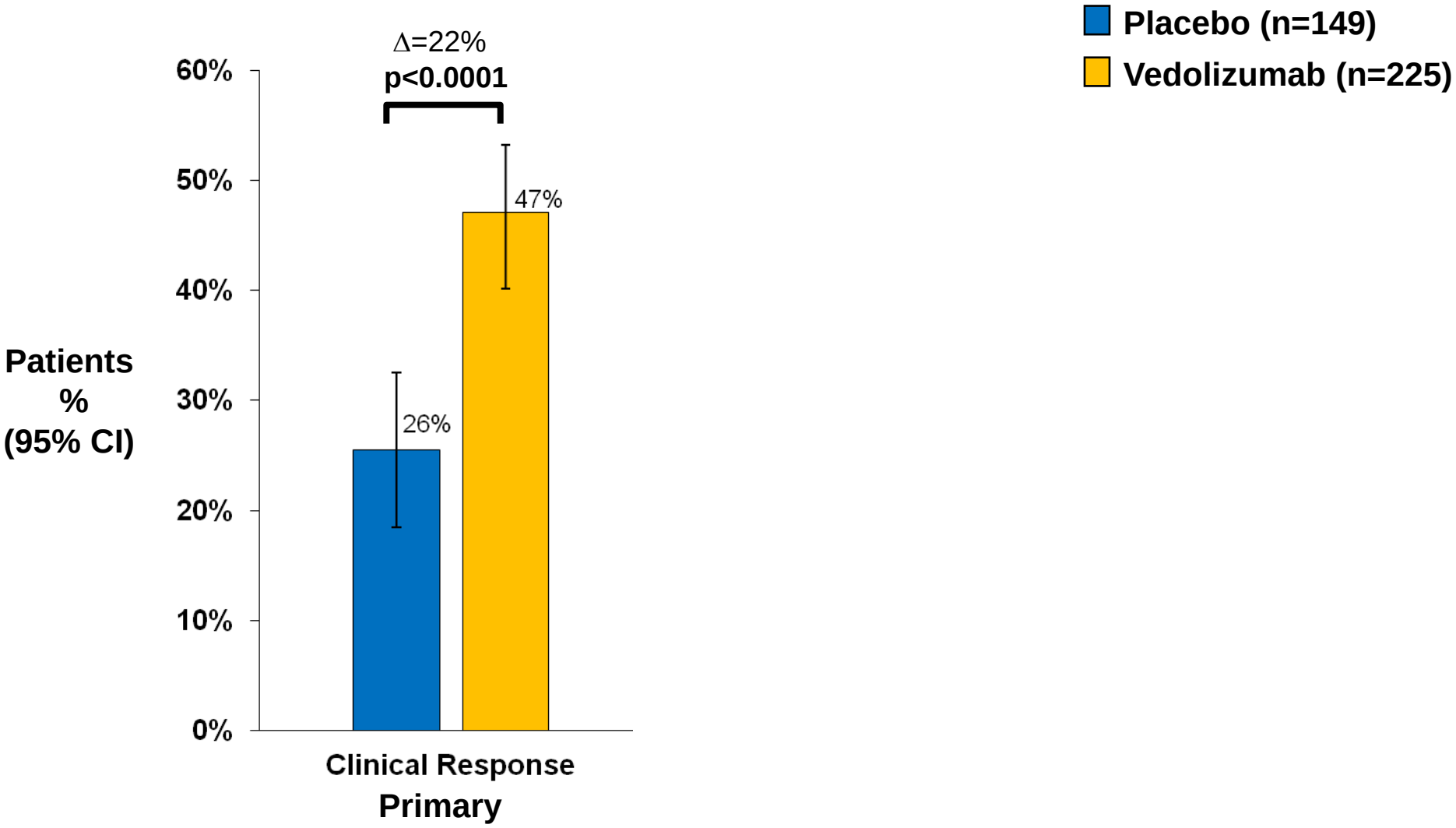
Criterion	Induction Study	Maintenance Study
Primary Endpoint	Clinical Response at Week 6	Clinical Remission at Week 52
Secondary Endpoints	Clinical Remission at Week 6 Mucosal Healing at Week 6	Clinical Response at Weeks 6 and 52 Mucosal Healing at Week 52 Clinical Remission at Weeks 6 and 52 Corticosteroid-free Remission at Week 52

UC (C13006)
Induction Results

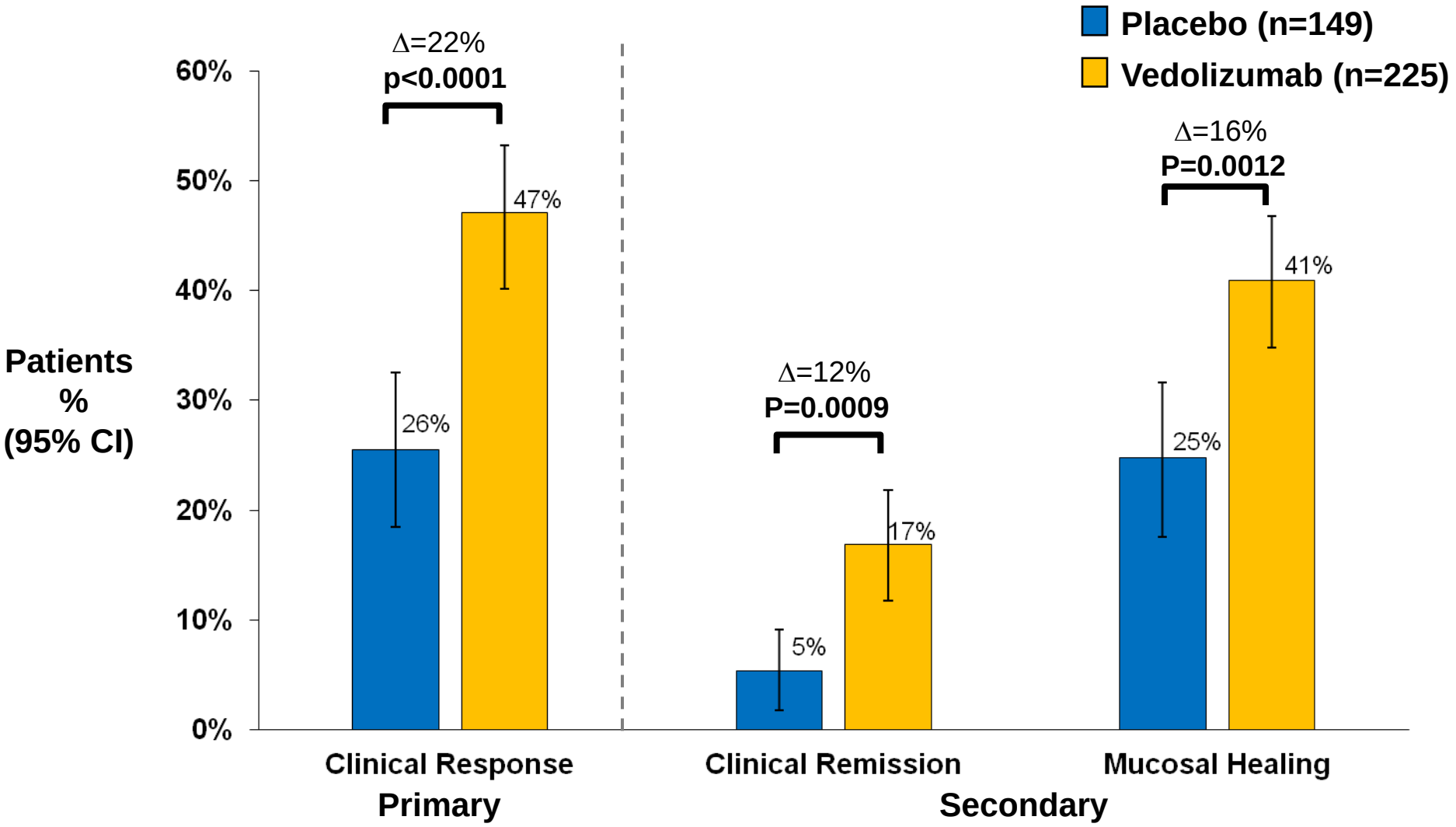
UC (C13006): Induction Demographics and Characteristics

Characteristic	Cohort 1		Cohort 2
	PBO (n=149)	VDZ (n=225)	VDZ (n=521)
Men	62%	59%	58%
Mean age, yrs	41	40	40
Race – White	77%	81%	84%
Region – North America	42%	35%	36%
Mean baseline Mayo score	8.6	8.5	8.6
Mean disease duration, yrs	7.1	6.1	7.2
Mean baseline fecal calprotectin, μg/g	2370	2552	1443
Concomitant corticosteroids	56%	56%	52%
Concomitant immunomodulators	30%	33%	36%
Prior anti-TNFα failure	42%	36%	43%
Prior immunomodulator use	72%	76%	77%

UC (C13006): Statistically Significant Primary Endpoint of Clinical Response

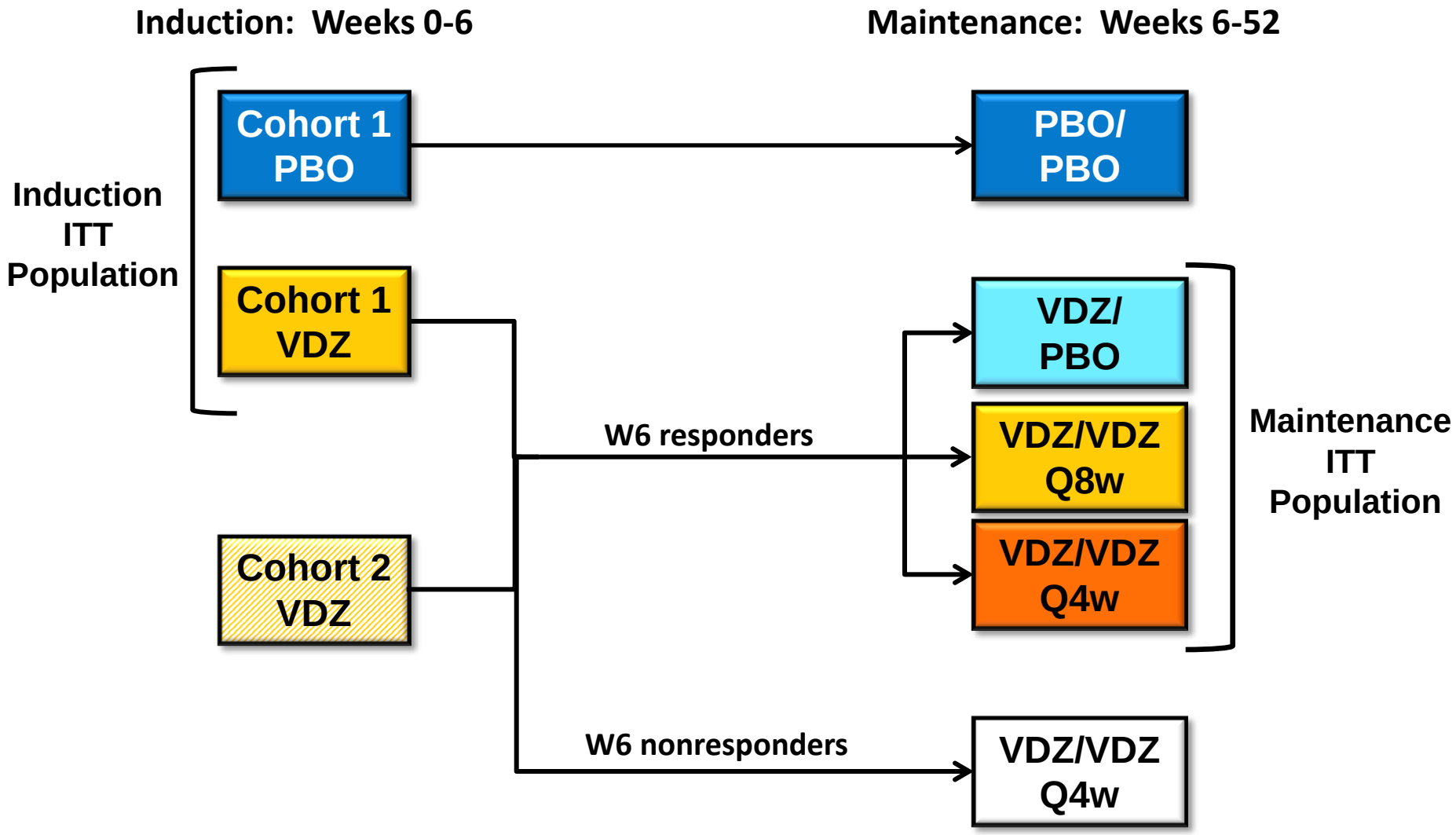


UC (C13006): Statistical Significance for All Induction Phase Endpoints

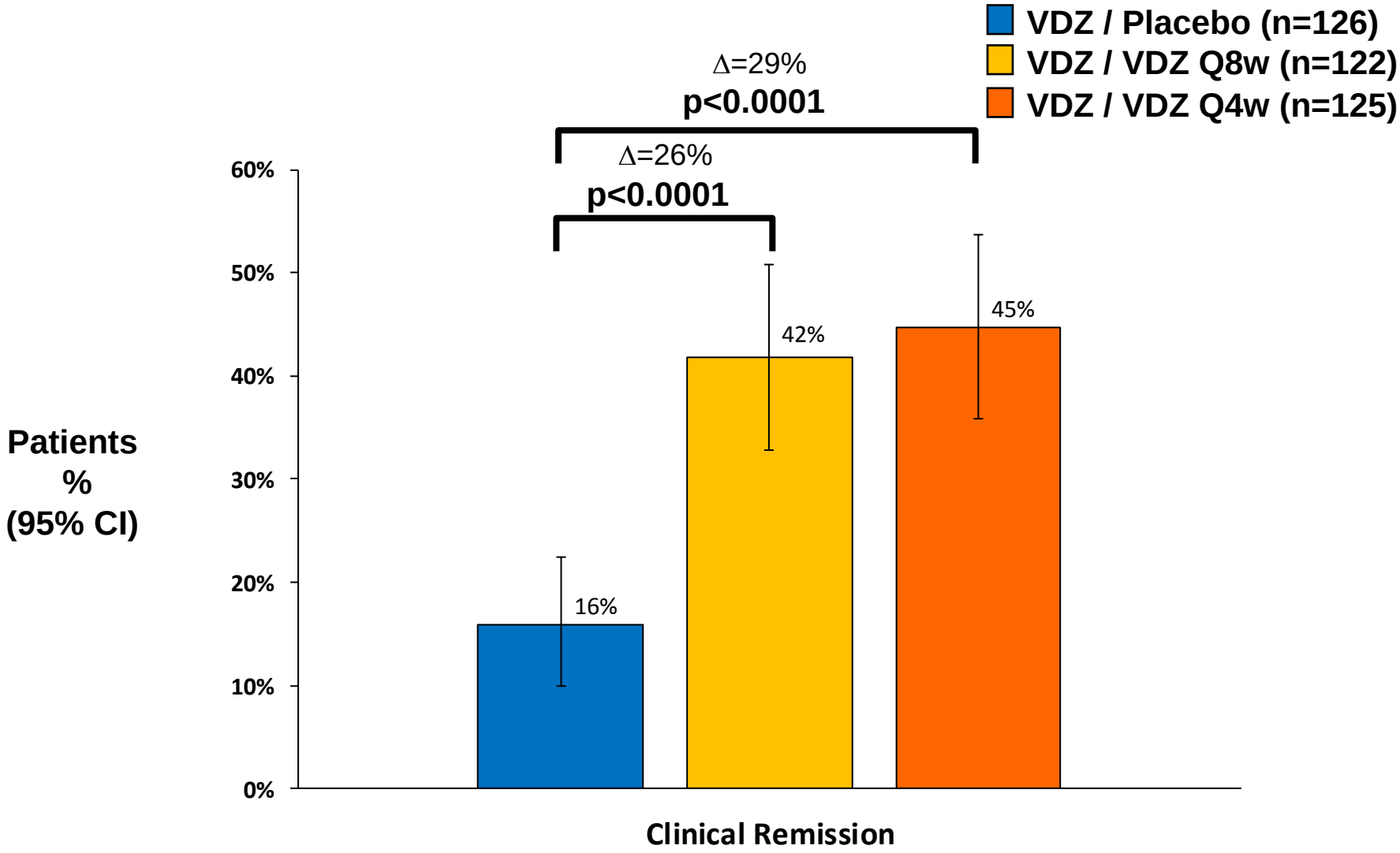


UC (C13006)
UC Maintenance Results

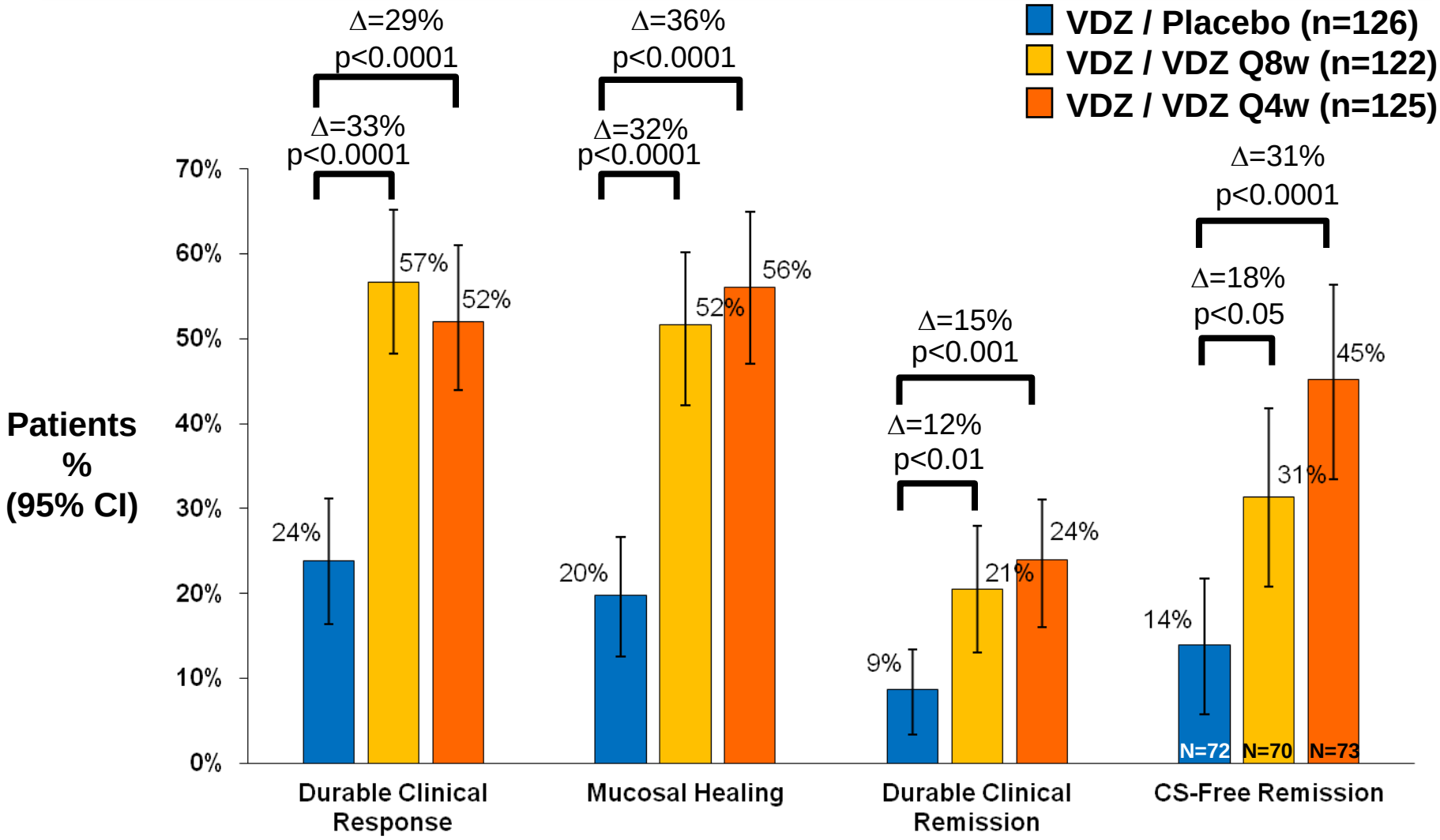
UC (C13006) Phase 3: Maintenance Study



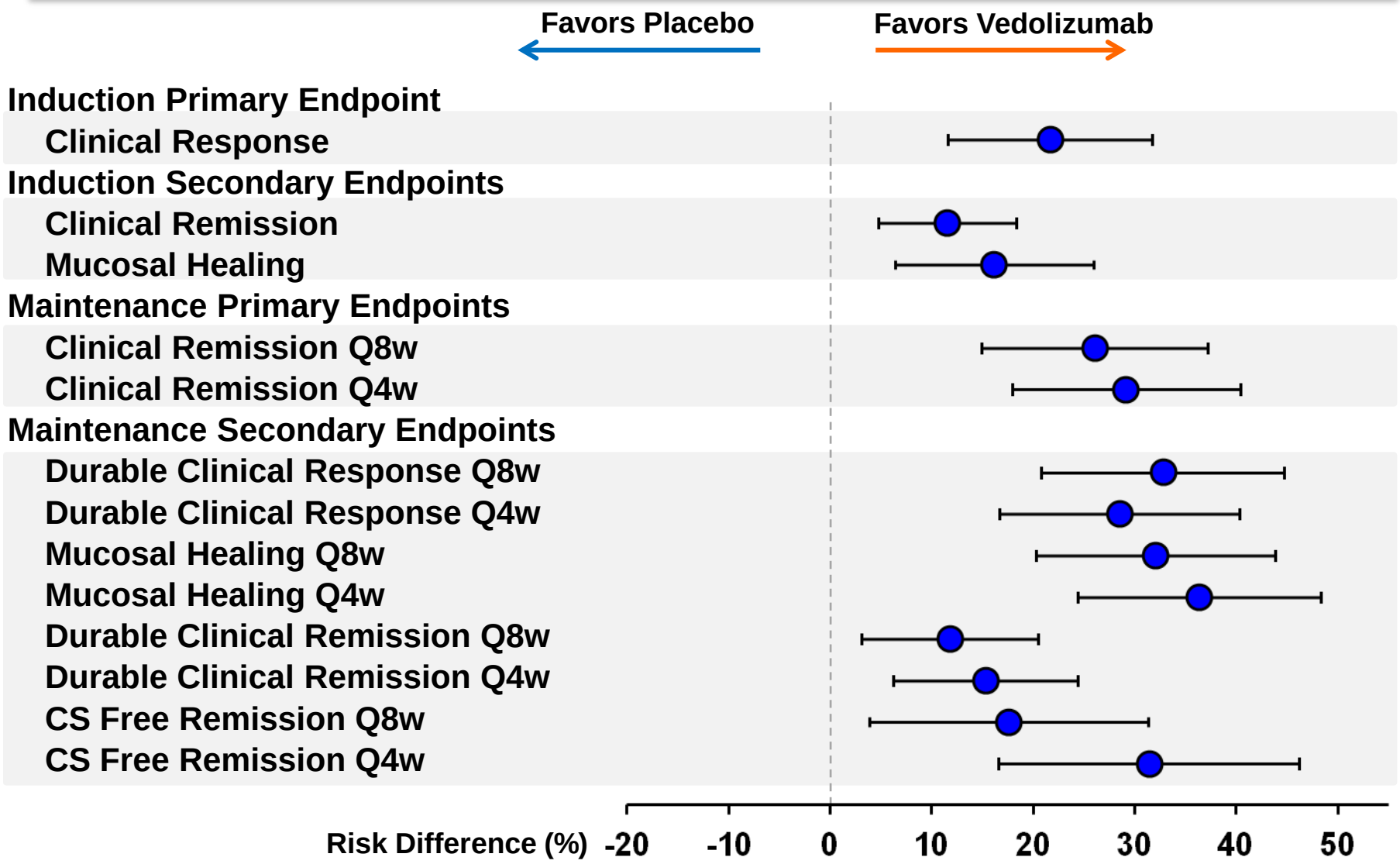
UC (C13006): Statistically Significant Effect on Remission Primary Endpoint at Week 52



UC (C13006): All Secondary Endpoints Achieved in Maintenance Study



UC (C13006): Vedolizumab Demonstrates Efficacy



Crohn's Disease Efficacy

Studies C13007 and C13011

Induction

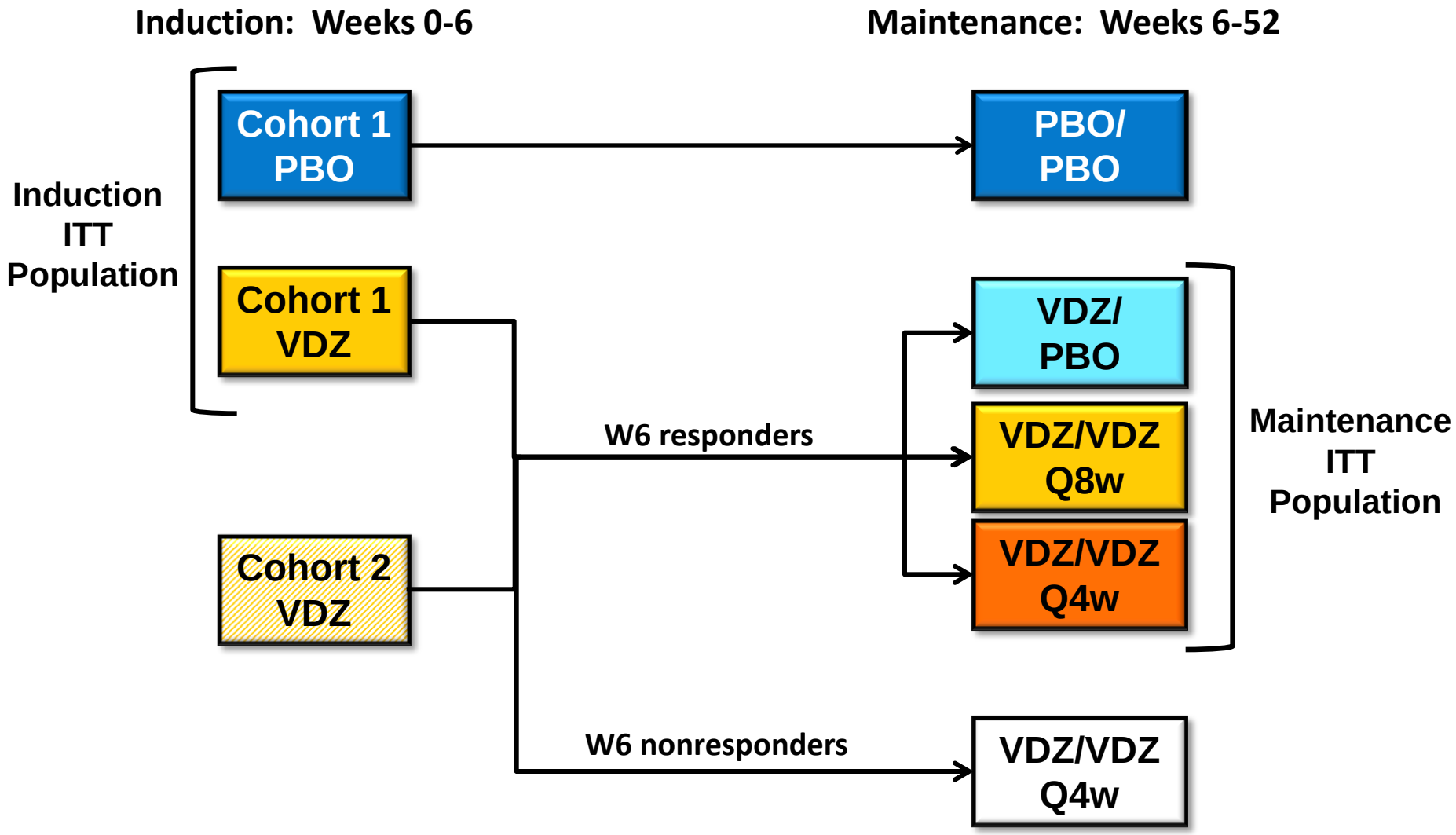
Study C13007

Maintenance

Phase 3 Studies Enrolled Moderately-to-Severely Active CD Patients

Criterion	CD (C13007 and C13011)
Disease Duration	≥ 3 months
Localization	Ileum and/or colon
Disease Activity	CDAI 220-450 (C13007) CDAI 220-400 (C13011) Active flare: ↑ CRP or ulcers or ↑ Fecal calprotectin plus supportive imaging
Prior Med Failure	Anti-TNFα AZA, 6-MP, methotrexate corticosteroids (ex-US)

CD (C13007): Same 52-week Trial Design as UC

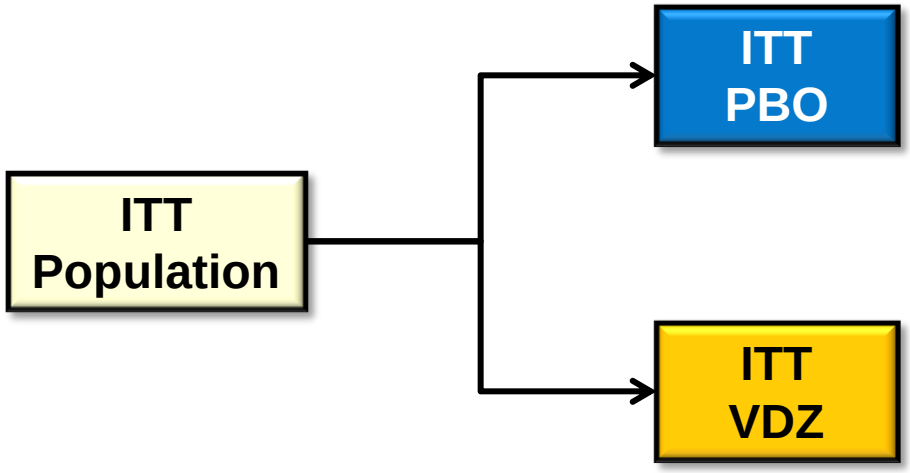


CD (C13007): Efficacy Endpoints for Induction and Maintenance Studies

Criterion	Induction Study	Maintenance Study
Primary Endpoint	Clinical Remission at Week 6 CDAI-100 at Week 6	Clinical Remission at Week 52
Secondary Endpoints	CRP reduction at Week 6	CDAI-100 at Week 52 Corticosteroid-free Remission at Week 52 Clinical Remission at ≥ 80% of visits and Week 52

CD (C13011): Phase 3 Induction Only Study

Induction: Weeks 0-10



Endpoints Assessed at Weeks 6 and 10

CD (C13011): Efficacy Endpoints for Induction Trial Focused on Anti-TNFα Failure

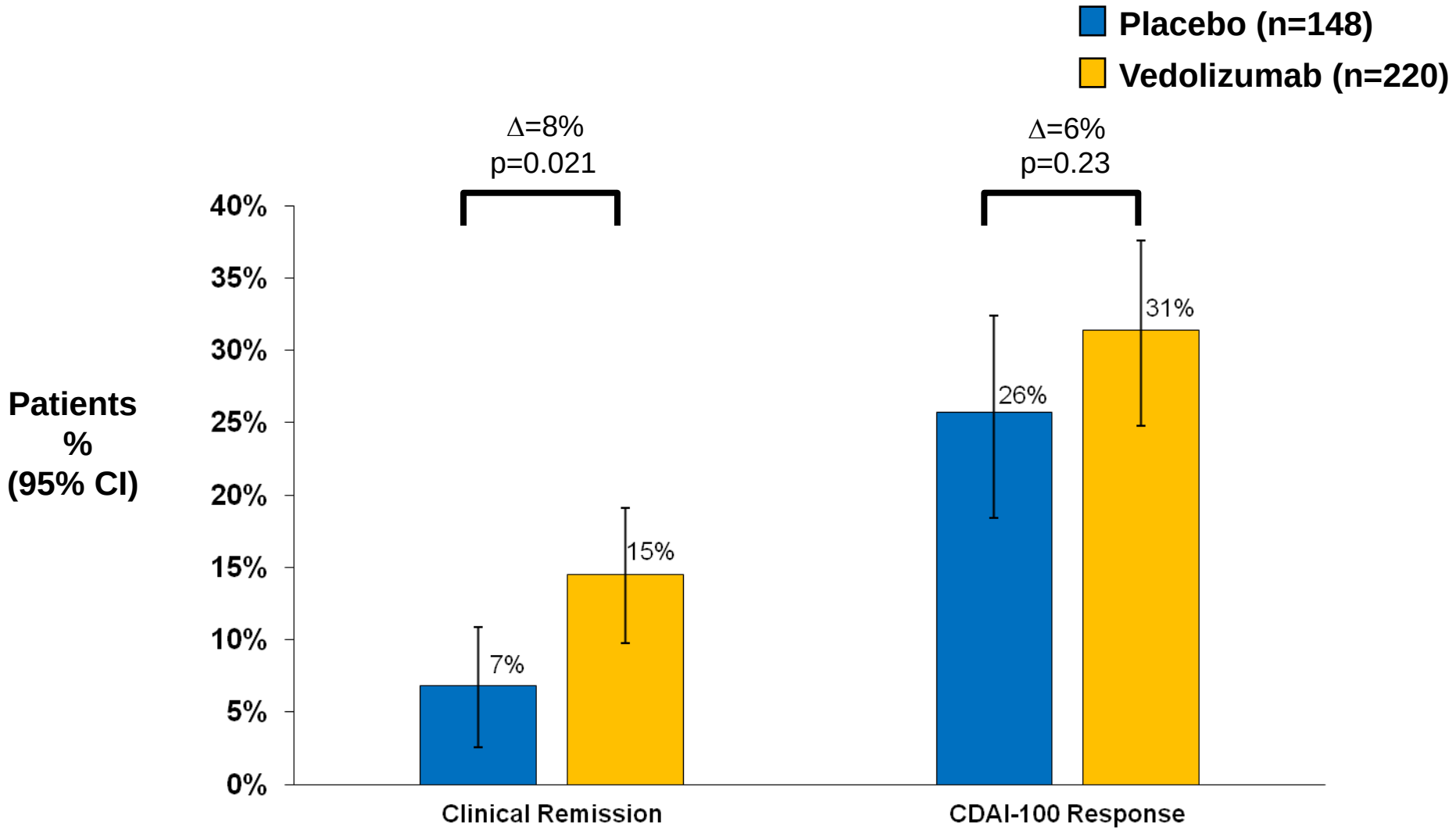
Criterion	Induction	
	TNFα Failures (75%)	Overall Population (100%)
Primary Endpoint	Clinical Remission at Week 6	
Secondary Endpoints		Clinical Remission at Week 6
	Clinical Remission at Week 10	Clinical Remission at Week 10
	Clinical Remission at Weeks 6 & 10	Clinical Remission at Weeks 6 & 10
	CDAI-100 Response at Week 6	

CD (C13007 and C13011) Induction Results

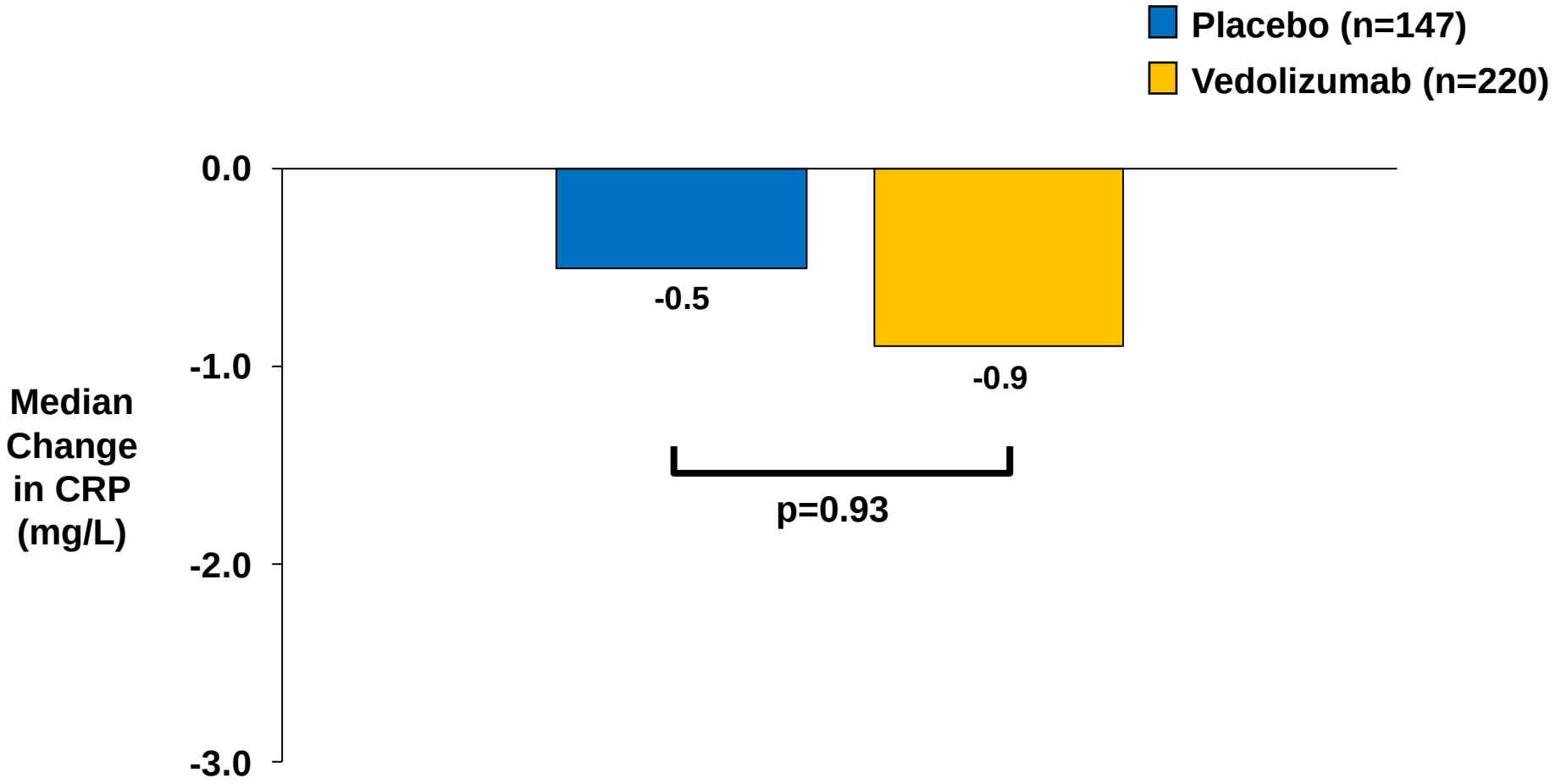
CD (C13007): Induction Demographics and Characteristics

Characteristic	Cohort 1		Cohort 2
	PBO (n=148)	VDZ (n=220)	VDZ (n=747)
Men	47%	48%	46%
Mean age, yrs	39	36	36
Race - White	84%	83%	92%
Mean baseline CDAI score	325	327	322
Mean disease duration, yrs	8.2	9.2	9.2
Median C-reactive Protein (mg/L)	13.7	15.3	10.2
History of prior surgery for CD	36%	45%	42%
History of fistulizing disease	38%	41%	35%
Concomitant corticosteroids	47%	47%	52%
Concomitant immunomodulators	34%	34%	33%
Prior failure of anti-TNFα	47%	48%	63%
Failed ≥ 2 anti-TNFα	28%	25%	0
Prior immunomodulator use	76%	79%	86%

CD (C13007): Statistically Significant Primary Endpoint of Clinical Remission



CD (C13007): Change in C-reactive Protein Levels at 6 Weeks Not Significant

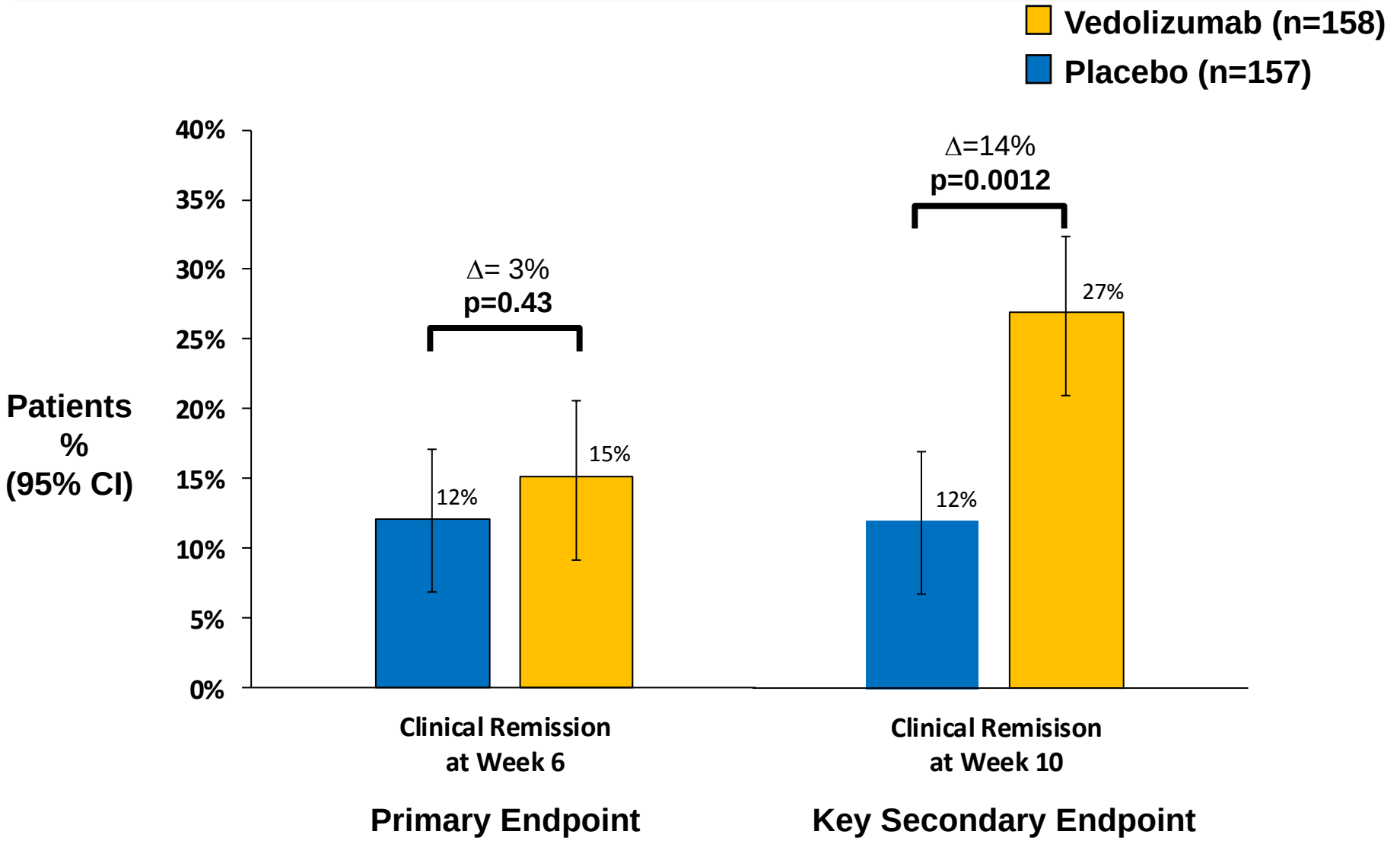


Mean Δ% vs PBO (95% CI)

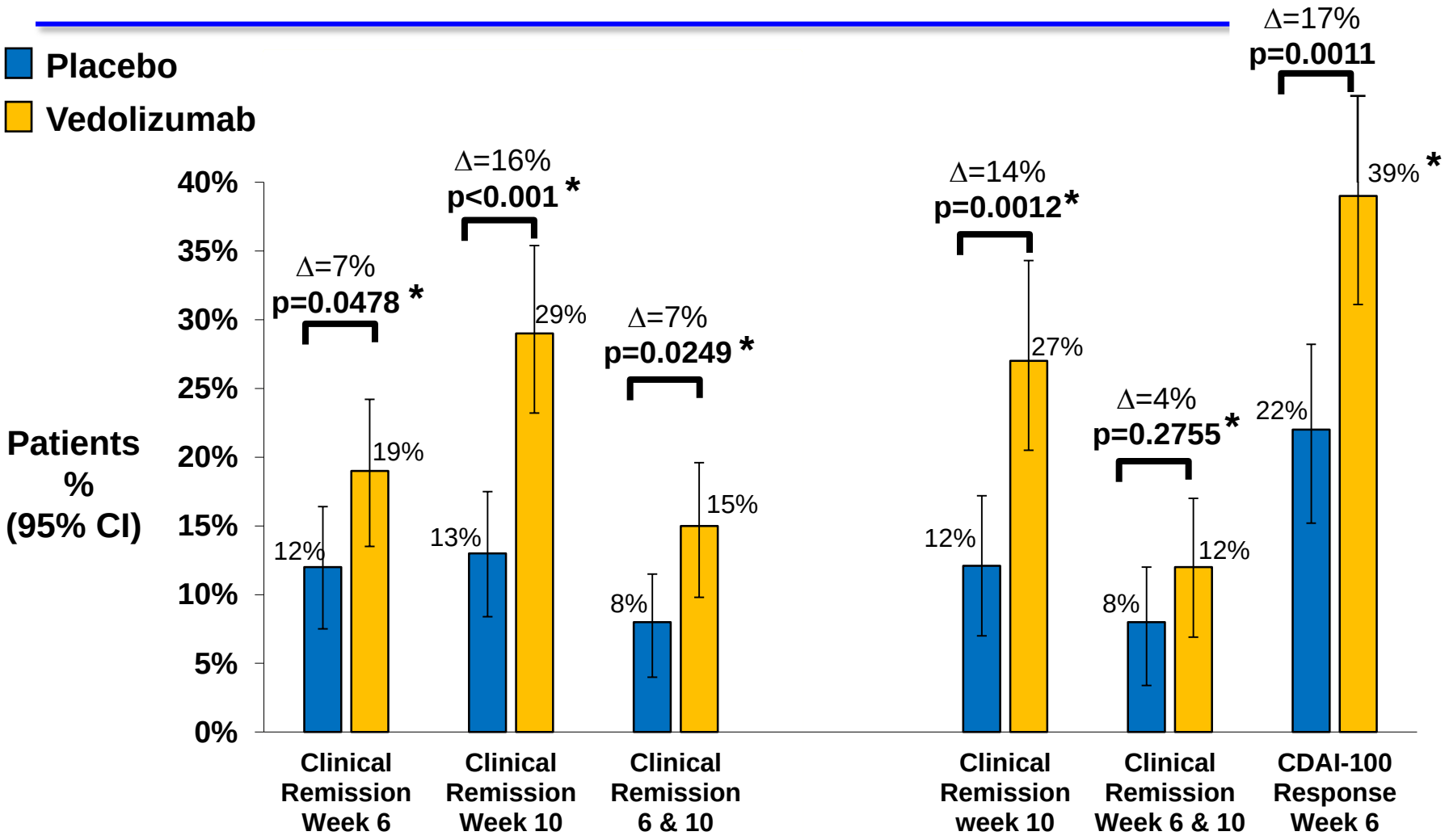
CD (C13011): Demographics and Characteristics

Characteristic	PBO (n=207)	VDZ (n=209)
Men	43%	44%
Mean age, yrs	35	37
Race - White	90%	90%
Mean baseline CDAI score	301	314
Mean disease duration, yrs	8.0	8.4
Median C-reactive Protein (mg/L)	18.5	19.0
History of prior surgery for CD	43%	44%
History of fistulizing disease	37%	34%
Concomitant corticosteroids	52%	53%
Concomitant immunomodulators	33%	34%
Prior anti-TNFα failure	76%	76%
Failed ≥ 2 anti-TNFα	45%	53%
Prior immunomodulator use	93%	84%

CD (C13011): Endpoints at Week 6 and Week 10 in Patients with Anti-TNFα Failure

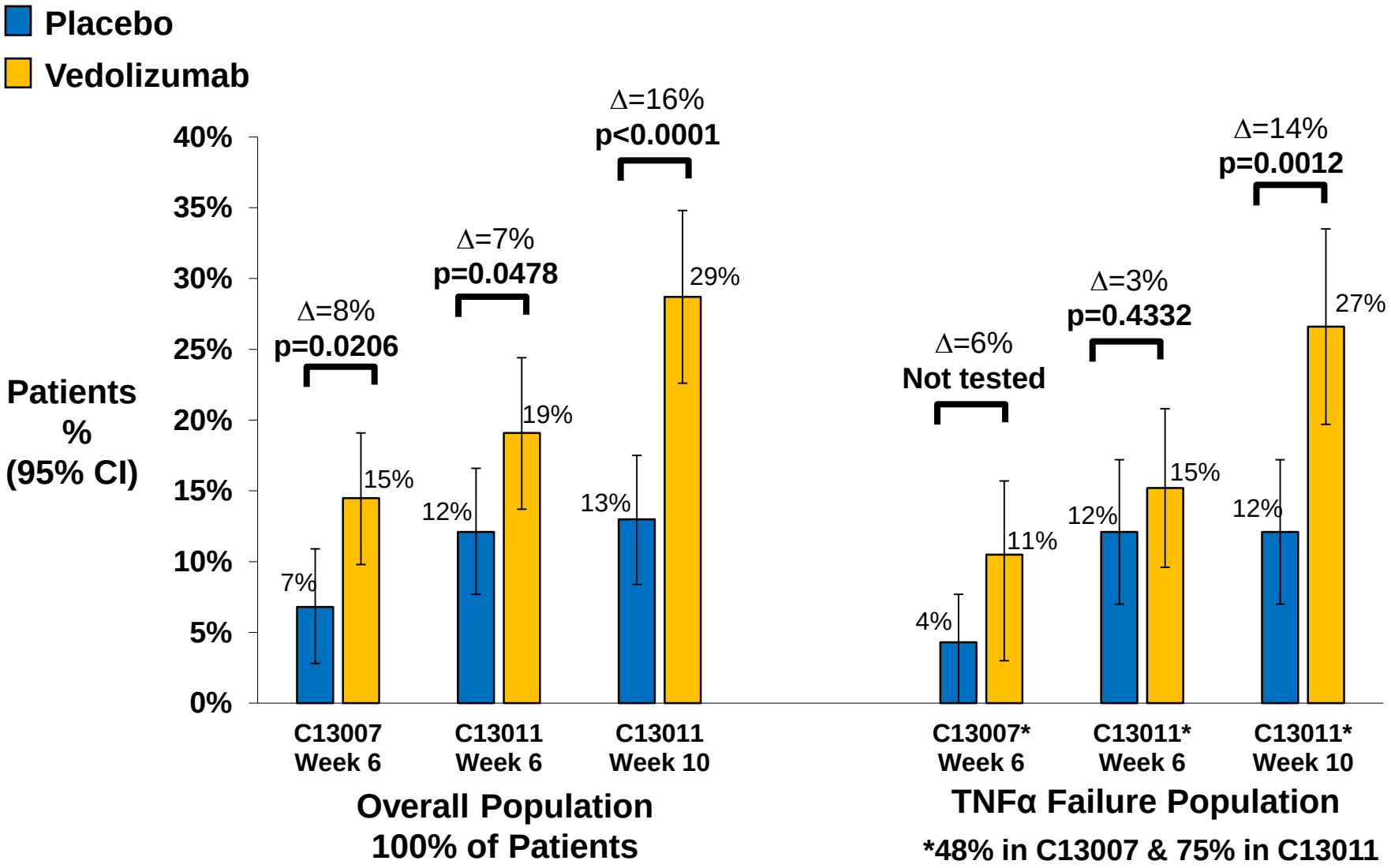


C13011 (CD): Secondary Endpoints



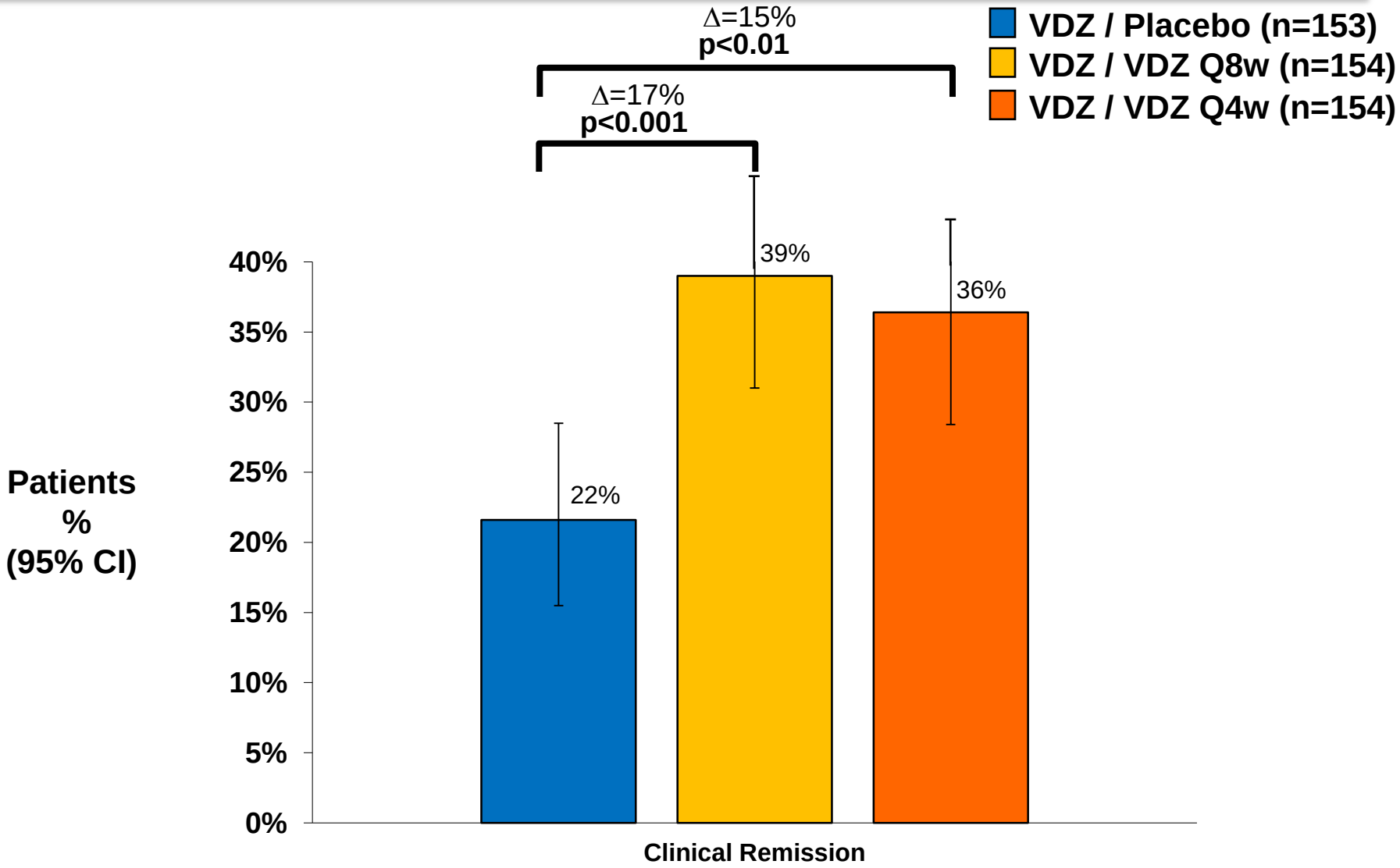
*Unadjusted

Clinical Remission at Week 6 in CD Study C13007 and at Week 6 and Week 10 in CD Study C13011

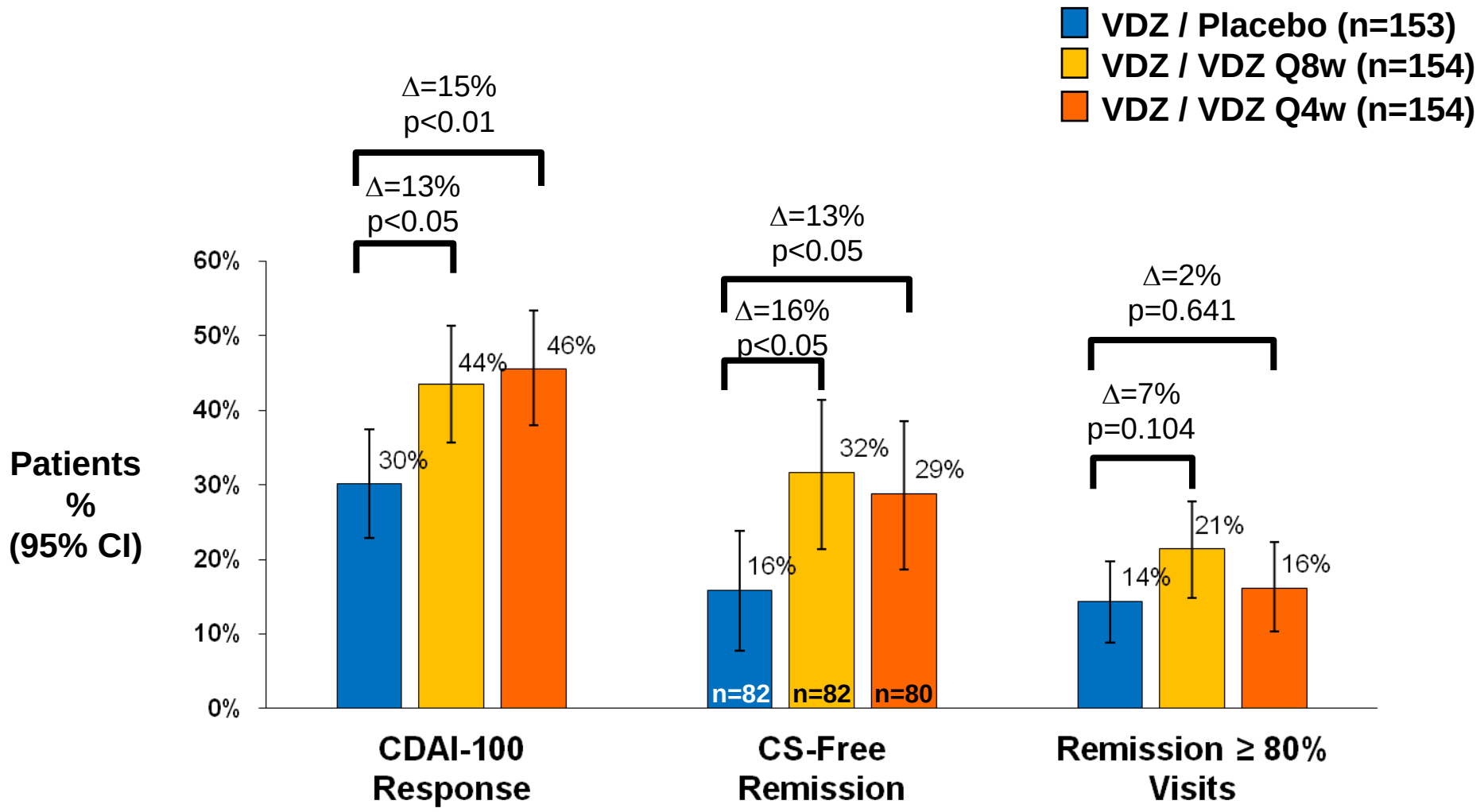


CD (C13007)
Maintenance Results

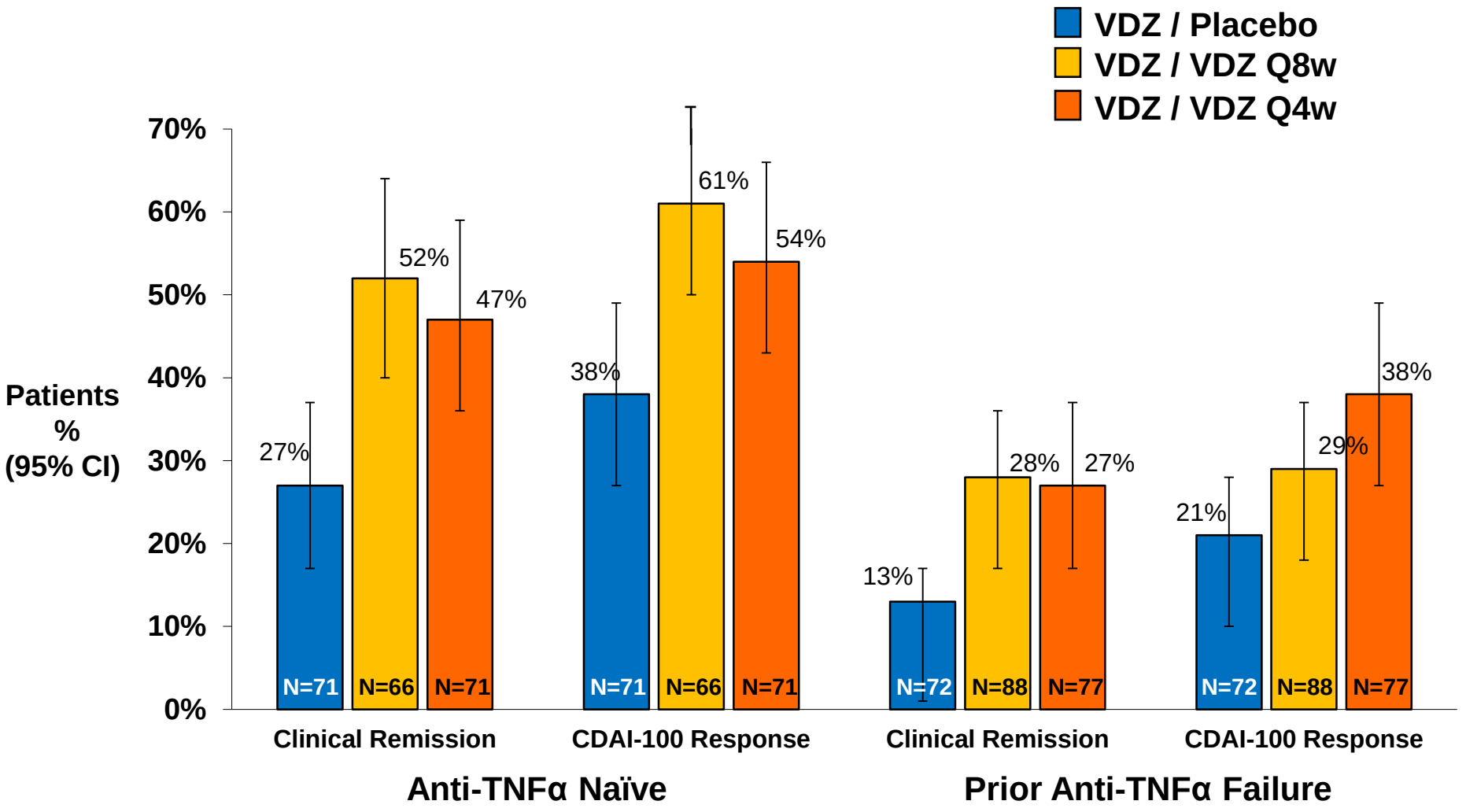
CD (C13007): Statistical Significance for Maintenance Primary Endpoint



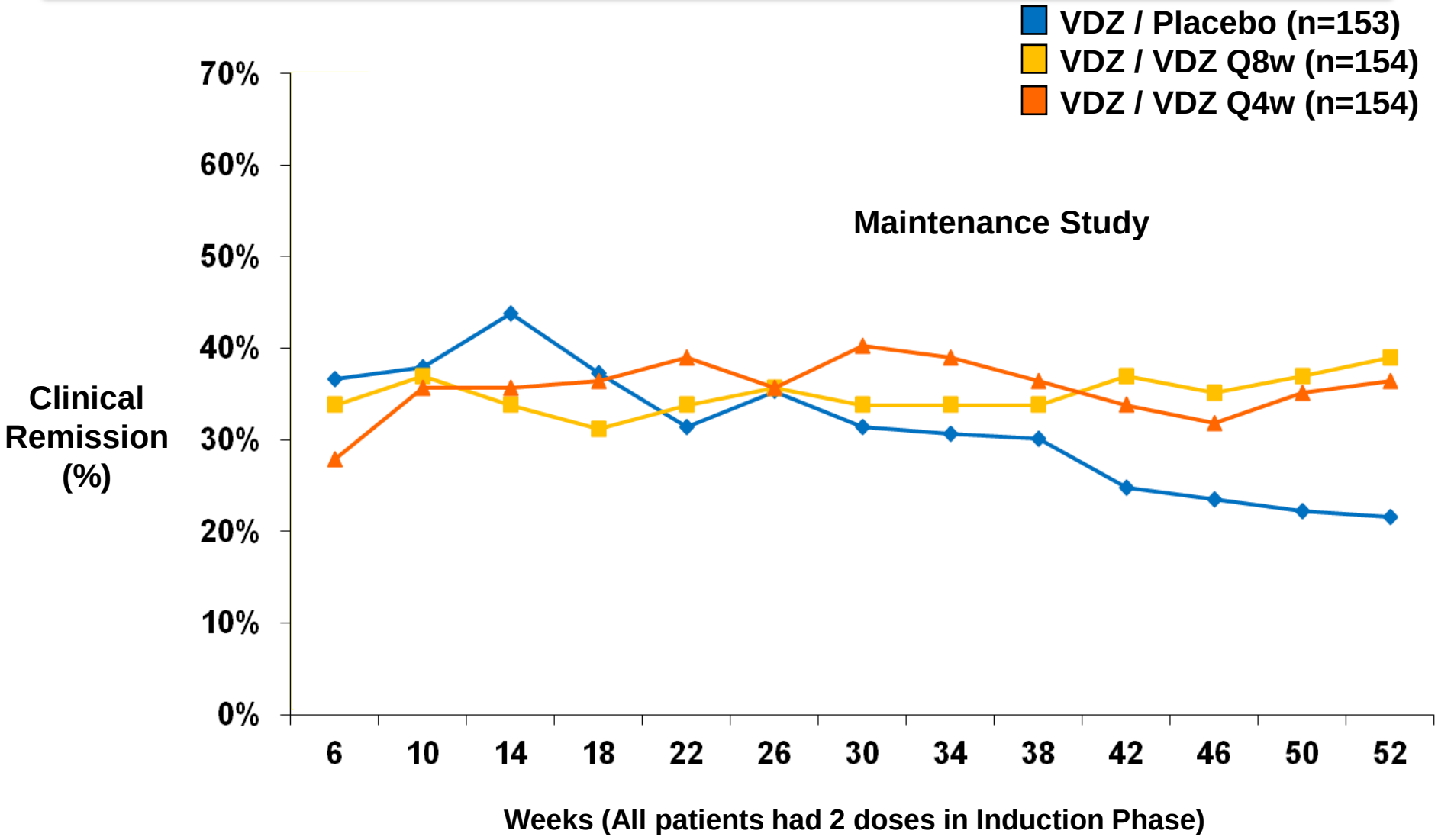
CD (C13007): Statistical Significance for CDAI-100 and CS-Free Remission at Week 52



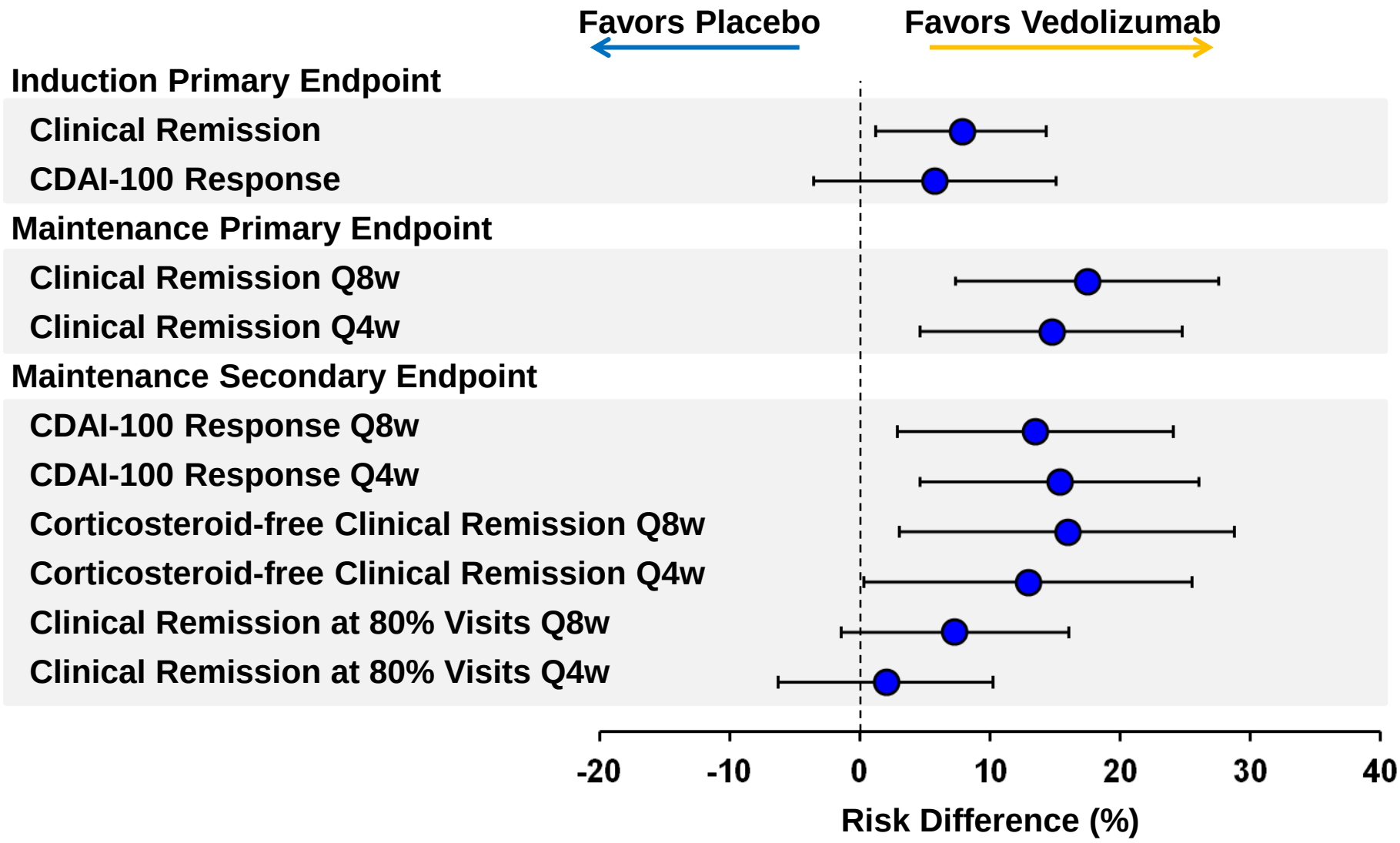
CD (C13007): Week 52 Remission & CDAI-100 Response by Prior Anti-TNFα Failure



CD (C13007): Clinical Remission More Likely in Patients Continuing VDZ



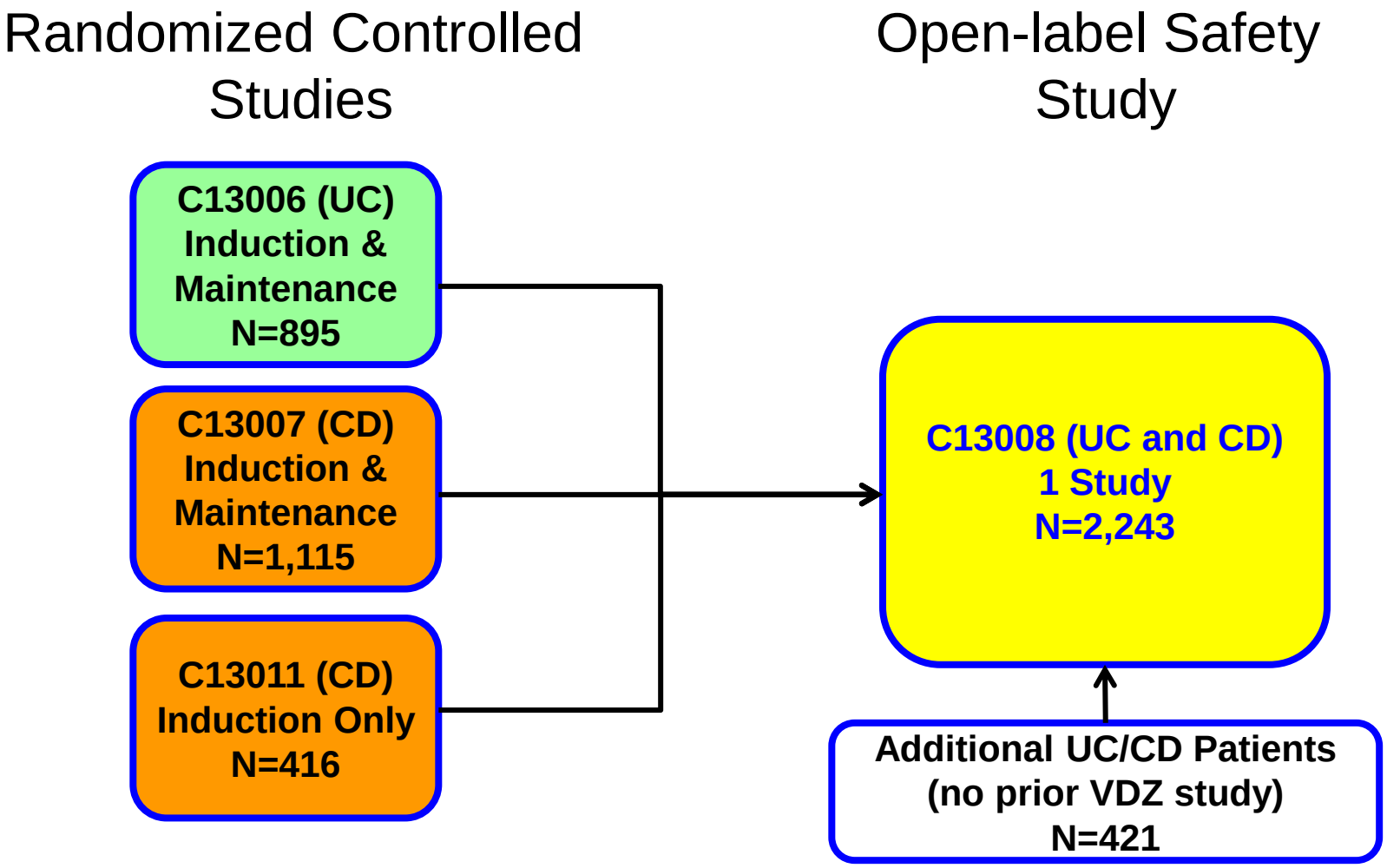
CD (C13007): Vedolizumab Demonstrates Efficacy in Crohn's Disease



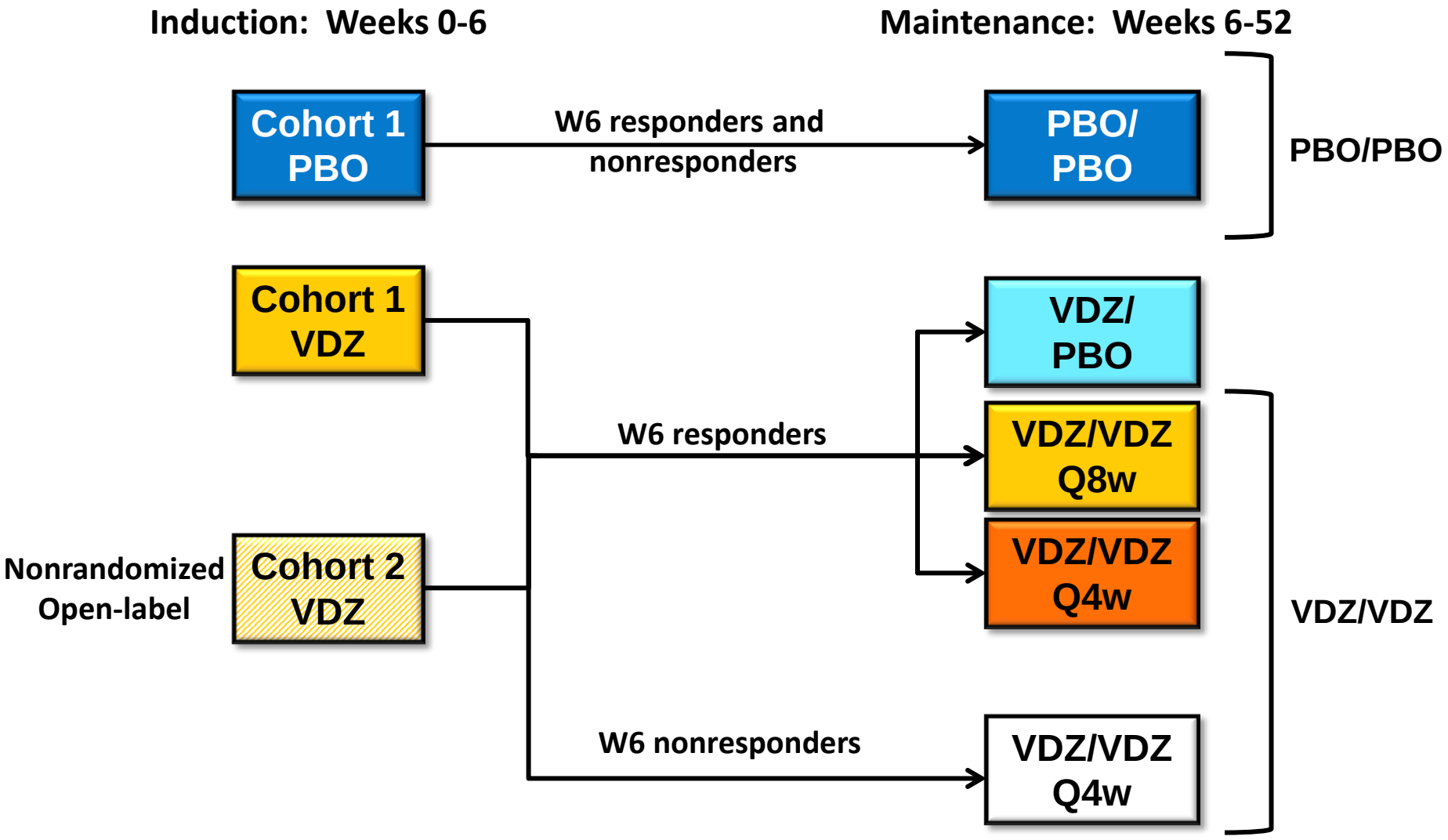
Vedolizumab Safety
1) Ulcerative Colitis
2) Crohn's Disease

Asit Parikh, MD PhD

Phase 3 Patient Flow



Safety Population: C13006 and C13007



Ulcerative Colitis
Safety

UC (C13006): Safety Summary from Placebo-controlled Study

Adverse Event Category (n)	52 Weeks PBO/PBO (n=149)	52 Weeks VDZ/VDZ (n=620)
Any AE	77%	80%
AE resulting in discontinuation	11%	6%
SAE	11%	12%
Serious infection	3%	2%
SAE resulting in discontinuation	4%	3%
Death	-	<1% (n = 1)

Death: arteriosclerosis coronary artery

UC (C13006): Serious AEs (≥ 1%)

Serious Adverse Event SOC Preferred Term	52 Weeks PBO/PBO (n=149)	52 Weeks VDZ/VDZ (n=620)
SAE	11%	12%
GI Disorders	8%	8%
Colitis ulcerative	7%	8%
Infections and Infestations	3%	2%

Crohn's Disease
Safety

CD (C13007): Safety Summary from Placebo-controlled Study

Adverse Event Category (n)	52 Weeks PBO/PBO (n=148)	52 Weeks VDZ/VDZ (n=814)
Any AE	80%	87%
AE resulting in discontinuation	9%	11%
SAE	16%	24%
Serious infection	3%	6%
SAE resulting in discontinuation	5%	7%
Deaths	<1% (n = 1)	<1% (n = 4)

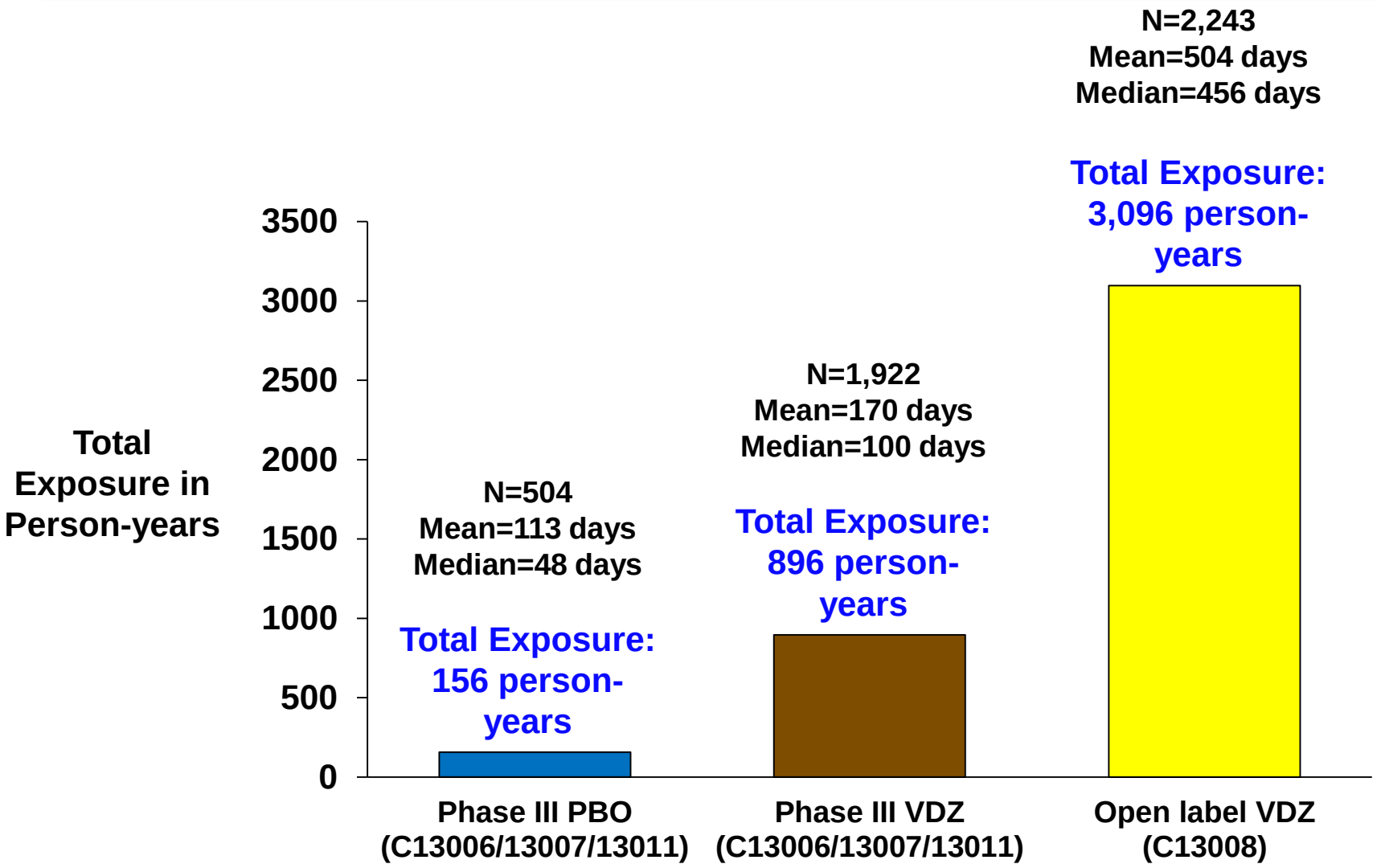
Deaths: bronchopneumonia, CD and sepsis, septic shock, intentional overdose, myocarditis

CD (C13007): Serious AEs (>1%)

SOC Preferred Term	52 Weeks PBO/PBO (n=148)	52 Weeks VDZ/VDZ (n=814)
SAE	16%	24%
GI Disorders	12%	16%
Crohn's disease	9%	12%
Infections and infestations	3%	6%
Anal abscess	<1%	2%

Safety Topics of Interest

Observation Time on Vedolizumab 25 Times That on Placebo (Pivotal + Long-term Safety)



HIRD* Retrospective Cohort Study

- Used to benchmark
  - Uncontrolled AE rates from C13008
  - Rare events
- Largest US commercially insured population
- Study population matched as closely as possible to vedolizumab Phase 3 program
- Limitations
  - US-based population
  - Endpoint definitions (ICD-9 vs MedDRA)

*HealthCore Integrated Research Database

Infections of Special Interest

Event	PBO Events/1000 Patient Yrs	VDZ Events/1000 Patient Yrs	HIRD Database Events/1000 Patient Yrs (95% CI)
C. difficile infection	0.00	7.11	3.14 (2.12 – 4.49)
Sepsis/ related terms[1]	9.35	2.50	6.20 (4.72 – 8.00)
Salmonella sepsis	0.00	0.21	0.00 (0.00 – 0.38)
CMV colitis	0.00	1.87	0.52 (0.17 – 1.21)
Salmonella infections	4.67	1.25	0.10 (0.00 – 0.58)
Tuberculosis	0.00	0.83	0.52 (0.17 – 1.21)
Viral meningitis	0.00	0.42	0.31 (0.06 – 0.91)
Listeria meningitis	0.00	0.21	0.00 (0.00 – 0.38)

[1]Includes the following MedDRA PTs: sepsis, septic shock, abdominal sepsis, bacterial sepsis, bacteremia and urosepsis

Liver Function Test Abnormalities: Placebo-controlled Studies

Analyte, n (%)	PBO/PBO (N = 297)	VDZ/PBO (N = 279)	VDZ/VDZ (N = 1,434)
ALT > 3 × ULN	3 (1)	6 (2)	22 (2)
AST > 3 × ULN	0	7 (3)	16 (1)
Bilirubin > 2 × ULN	2 (< 1)	2 (< 1)	7 (< 1)
Hy's Law (ALT > 3 x ULN and bili > 2 x ULN)	0	0	0

6 Patients Reported 7 Hepatitis SAEs in 3,129 UC and CD VDZ Patients

Study	Age/Sex	SAE Preferred Term	Comment	Days from 1st/Last dose
Placebo-controlled Studies				
UC	28 / F	Hepatitis acute	15 wks pregnant diagnosed with autoimmune hepatitis during long-term follow-up	564/212
	20 / M	Hepatitis acute	Liver bx – diagnosed with chronic autoimmune hepatitis, pharmacologic cause “less likely”	155/57
CD	23 / F	Cytolytic hepatitis	Nodular regenerative hyperplasia on liver bx. Associated with thiopurines	36/22
	35 / F	Hepatitis	Liver bx consistent with 5-ASA allergic rxn	54/41
Open-label C13008				
UC	37 / F	Hypertransaminasaemia; Hepatitis acute*	IgG strongly (+) for Ro52 and anti-SLA/LP; prompt response to steroids; later diagnosed with cutaneous lupus	596/32
CD	33 / M	Hepatic enzyme increased	Liver bx – low grade steatohepatitis with fibrosis. Remains on study and LFTs normalized	261/2

*Originally reported as “liver failure”

18 Malignancy SAEs

Study	Age/Sex	Neoplasm	# VDZ Doses
Placebo-controlled Studies			
UC	73 / M	Colon Cancer	2
	40 / M	Transition Cell Carcinoma	2
	32 / M	Colon Cancer	7
CD	45 / F	Breast Cancer	2
	52 / F	Squamous Cell Carcinoma	10
	20 / F	Carcinoid of Appendix	13
Open-label			
UC	47 / M	Malignant Melanoma	2
	75 / F	Lung Neoplasm	4
	63 / M	Breast Cancer *in situ*	6
	44 / M	Metastases to peritoneum	8
	70 / M	Malignant Melanoma	9
	50 / M	Renal Cancer	29
CD	69 / F	Lung Neoplasm	3
	45 / F	Colon Cancer	8
	46/ M	Basal Cell Carcinoma	12
	42 / M	B-Cell Lymphoma	21
	49 / M	Squamous Cell Carcinoma	37
	51 / F	Hepatic Neoplasm	41

14 Deaths in 3,129 UC and CD Patients

IBD	Age/Sex	Arm	Days From 1st/Last Dose	# VDZ Doses	Preferred Term
Placebo-controlled Studies					
UC	66 / M	VDZ	14 / 14	1	Coronary arteriosclerosis
CD	23 / M	VDZ	88 / 75	2	Myocarditis
	31 / M	VDZ	98 / 28	4	Septic shock
	28 / M	VDZ	260 / 45	5	CD, Sepsis
	47 / F	VDZ	97 / 6	5	Intentional overdose
	75 / M	PBO	-- / --	n.a.	Bronchopneumonia
Open-label					
UC	49 / F	VDZ	332 / 50	4	Respiratory failure
	71 / F	VDZ	195 / 111	5	Cerebrovascular accident
	79/ M	VDZ	362 / 26*	11	West Nile Virus
	72 / M	VDZ	883 / 16	17	Pulmonary embolism
CD	32 / M	VDZ	125 / 125	1	Sepsis
	38 / M	VDZ	380 / 98	7	Completed suicide
	64 / M	VDZ	387 / 23	14	Traumatic intracranial hemorrhage
	51 / F	VDZ	1193 / 58	42	Hepatic malignancy

*Preliminary data

Extensive Exposure Data With Concomitant Immunomodulators

Months of Immunomodulator Exposure	Number of Patients with Concomitant Immunomodulators Use		
	UC (N=282)	CD (N=468)	UC + CD Combined (N=750)
≥ 12 months	155	268	423
≥ 24 months	119	129	248
≥ 36 months	24	38	62

Patients enrolled in C13006, C13007, C13011, C13008

Vedolizumab Infection SAEs by Baseline Concomitant Medications

High Level Term	VDZ/VDZ			
	No ConMed (n=445)	CS Only (n=506)	IMM Only (n=247)	CS+IMM (n=236)
Patients with Infection SAE	4%	3%	5%	4%
Abdominal and GI infections	3%	2%	3%	2%
Sepsis, bacteraemia, viraemia & fungaemia NEC	<1%	<1%	0	<1%
Lower respiratory tract and lung infections	<1%	<1%	<1%	<1%
Infections NEC	0	<1%	<1%	0
Bacterial infections NEC	<1%	<1%	0	0

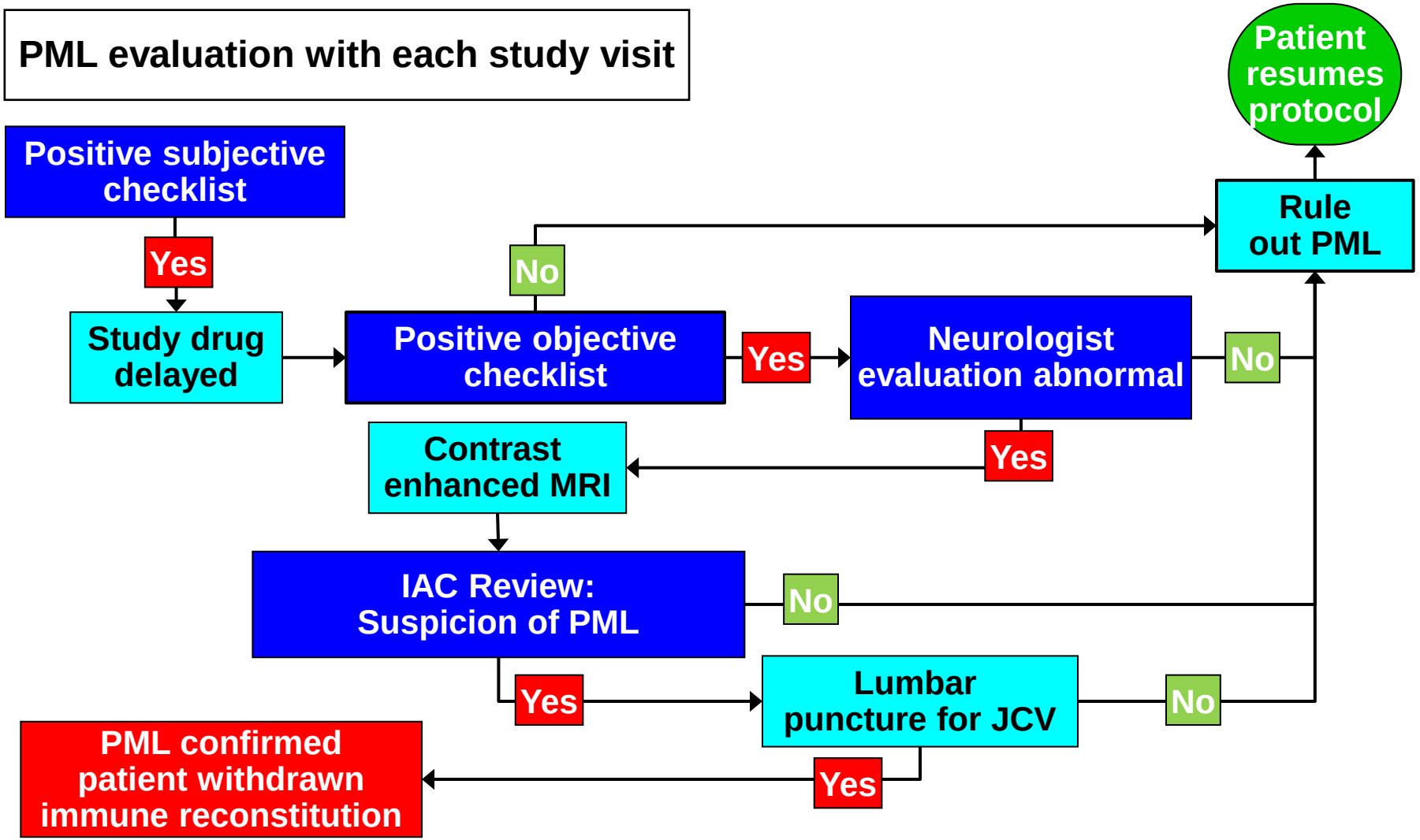
HLTs with at least 2 events in any group are shown

Overall Safety in Patients With Moderate-to-Severely Active UC or CD

- Most common AEs self-limited
- Infections more frequent with vedolizumab
  - Most common infections were mild-to-moderate and resolved with treatment
  - GI infections responded to treatment during continued vedolizumab exposure
- AEs profile stable through 48 months
- No increase in rates of infection with concomitant immunomodulator use

PML Risk Assessment for Vedolizumab

Systematic Evaluation Using PML Algorithm & Independent Adjudication

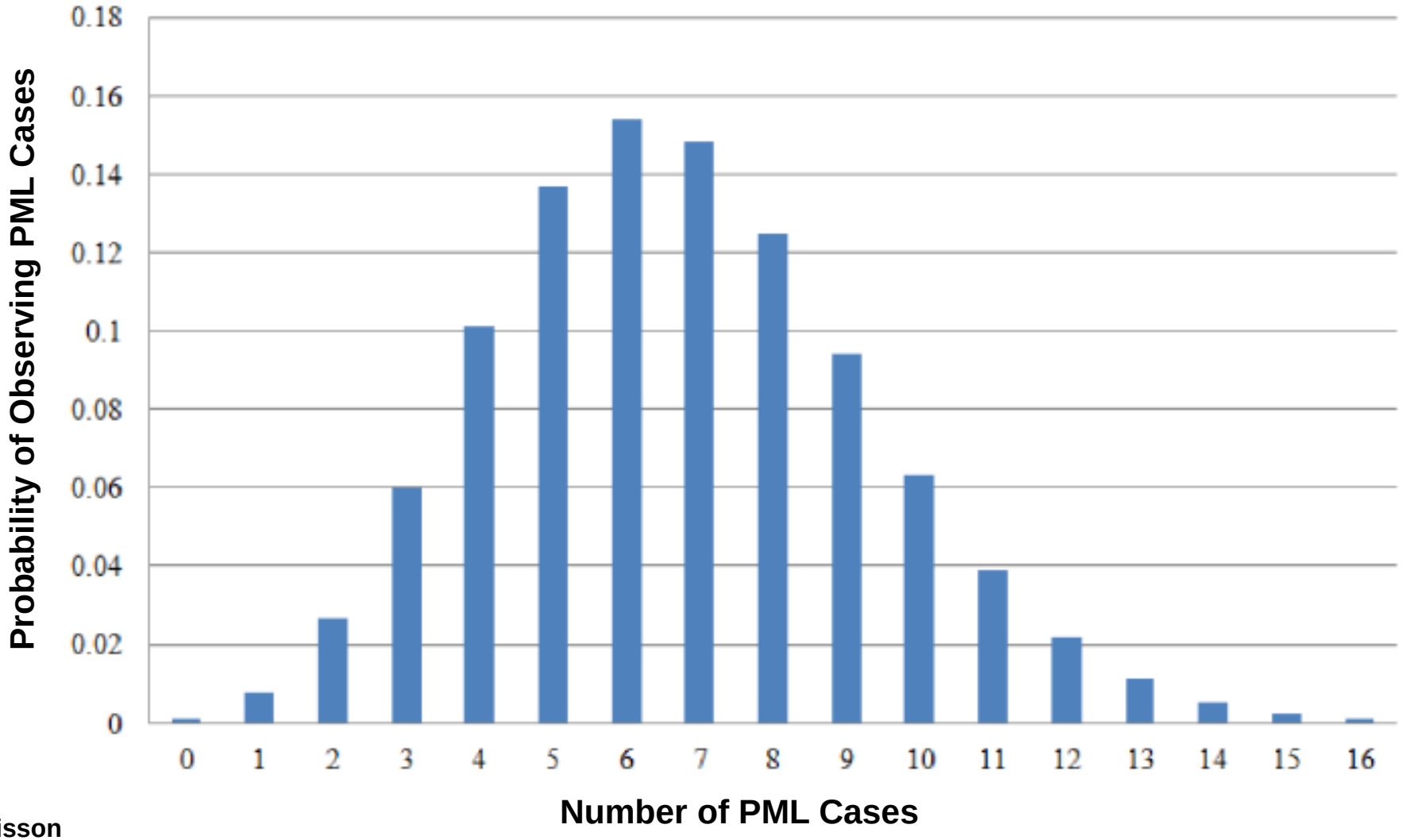


IAC = independent adjudication committee

RAMP Experience Since 2007

RAMP Findings % of patients	Total VDZ (n=2,927)
Screening at Each Visit	98%
Positive (Subjective)	10%
Positive (Objective)	10%
Neurological Consult	3%
Independent Adjudication Committee Review	3%
MRI	2%
Lumbar Puncture	<1%
PML Diagnosis	0%

Probability of Observing PML Cases With Vedolizumab if Risk Similar to Natalizumab



Poisson

An Assessment of the Risk of PML With Vedolizumab

Joseph Berger, MD

Ruth L. Works Professor and Director of MS Clinic, Department of Neurology, University of Kentucky, KY

Pathogenesis of PML

- Initial infection with archetypal JC virus
  - JCV found in >50% of population
- Establishment of latent or persistent infection
- Emergence a pathogenic neurotropic strain
  - Gene re-arrangement in JCV promoter region
- Entry of JCV into brain and establishment of productive oligodendrocyte infection
- Failure of JCV-specific T lymphocytes to clear reactivated virus from the brain

PML Risk Dependent on JCV Re-arrangement & Immune Impairment

- Factors that increase risk for PML with natalizumab
  - JCV antibody seropositivity
  - Prior immunosuppressive therapy
  - Longer treatment duration
- These risk factors are applicable to both MS and CD patients

Incidence of PML With Natalizumab

- Overall PML events in Sept. 2012[1]
  - 285 cases
  - 2.63 / 1000 patients (95% CI: 2.2 - 2.9)
- Current overall PML events (Sept. 2013)[2]
  - 399 cases
- Natalizumab appears to be the sole driver of PML

1. Baldwin, Curr Opin Neuro (2013); 2. Wuethrich, J Neuropathol Exp Neurol (2013)

PML Association With Natalizumab Linked to $\alpha_4\beta_1$ / VCAM-1 Pathway

1. Impairs the immune surveillance of the CNS
2. Release of premature B cells from bone marrow stores
   - Transactivation of JCV by upregulated transcriptional factors
   - Rearrangement of the promoter region of JCV genome to neurotropic virus

Vedolizumab MOA

- Solely an $\alpha_4\beta_7$ integrin inhibitor without activity on $\alpha_4\beta_1$
  - No JCV viremia with vedolizumab
  - No release of premature B cells
  - No effect on CNS inflammation
    - EAE study in Rhesus monkeys
  - No effect on CNS lymphocyte subpopulations

Parikh A et al: Digestive Dis Week, New Orleans, (May 1, 2010); Milch C, et al: J Neuroimmunol in press

PML Has Distinct Signs and Symptoms

- PML is a progressive disorder; it is not a subtle disease
- One can monitor for the symptoms and signs of PML
  - Cognitive and behavioral abnormalities
  - Hemiparesis
  - Paresthesiaes and numbness
  - Language and speech problems
  - Visual disturbances
  - Incoordination and gait disorders

Vedolizumab PML Surveillance

- Risk Assessment & Minimization for PML (RAMP)
  - Independent Adjudication Committee
- Algorithm included neurological referral following relevant neurological complaint during screening
- No cases of PML identified

Takeda Has Rigorously Investigated the Potential Risk of PML With Vedolizumab

- $\alpha_4\beta_7$ is gut-selective
  - No impairment of CNS immunosurveillance
  - No effect on premature B cells
- By its mechanism of action and by available clinical data, the risk of PML appears very low
- The risk of PML with vedolizumab should not be conflated with that of natalizumab

Vedolizumab Risk Management Program

Lesley Wise, PhD

VP Risk Management and Pharmacoepidemiology

Takeda Development Centre Europe, Ltd.

Vedolizumab Risk Management Program: Extension of Clinical Development Program

- Identified safety concerns
  - Infusion-related reactions
  - Upper respiratory tract infection (URTI)
- Potential safety concerns
  - Serious/opportunistic infections
  - Malignancy
- RAMP confirmed no cases of PML

Goals of Risk Management Program

- Inform and Educate HCPs and Patients
  - Known/potential risks: infusion reactions, URTI, serious infections, malignancy, PML
- Continue to gather data
  - Long-term extension study (C13008)
  - Voluntary long-term observational study
    - Real-world experience
- Monitor for new safety signals
  - Ensure patient safety

Risk Management for Vedolizumab

	USPI	REMS & Med Guide	Post-marketing Safety Study	C13008
Infusion-related reaction	✓	✓	✓	✓
URTI	✓	✓	✓	✓
Serious infection including opportunistic	✓	✓	✓	✓
Malignancy	✓	✓	✓	✓
Pregnancy	✓	✓	✓	✓
PML	✓	✓	✓	✓
Prior natalizumab exposure	✓	✓	✓	

Post Authorization Observational Study

OBJECTIVE

- Add long-term biologic comparator data
- Investigate long-term safety, and characterize
  - Infusion-related reaction
  - Infections
  - Malignancies
  - Pregnancy

DESIGN

- Anticipated duration 7 years
- Multinational
- 2,500 patients on vedolizumab
- 2,500 patients on other biologics
- ~4,700 patients on vedolizumab when combined with C13008

BENEFIT

- Real-world use and safety
- Interim analyses as study progresses
- Experience in patients with prior natalizumab exposure

C13008: Long-term Extension Study

OBJECTIVE

- Additional long-term safety data, particularly to further characterize reports of infections and malignancies

DESIGN

- Open-label
- Multinational
- Run through 2016
- 2,243 patients on VDZ

BENEFIT

- Patients already enrolled
- Long-term safety data available during early post-marketing period

Monitoring Infusion-related Reaction (IRR)

- IRRs in clinical program were infrequent and usually mild/moderate
- Observational study will provide characterization of the events
- Spontaneous reporting will allow detection of the more severe events

Vigilance for Changes in Infection Frequency and/or Severity

- Infection frequency and severity characterized in the observational study and long-term extension study
- Comparative infection rates with biologic therapies available from the observational study
- Spontaneous reporting for characterizing rare and/or severe infections

Characterizing Malignancies

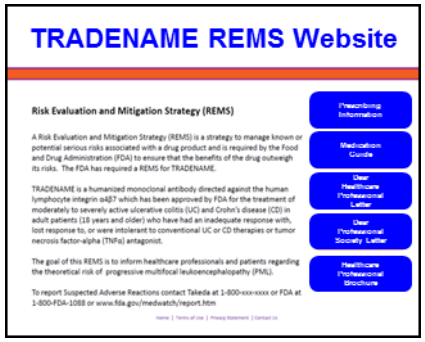
- Current exposure adjusted data do not suggest an increased risk
- Additional long-term data will add further clarity
- Comparator data will allow benchmarking against other therapies

Monitoring Neurological Events

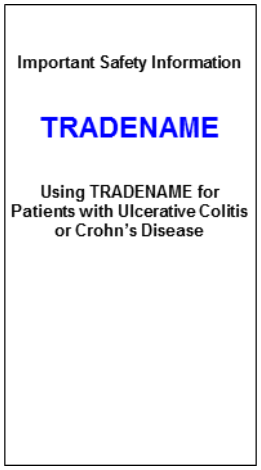
- PML was a major focus of our risk management in clinical trials
  - No PML observed
  - Cannot rule out risk
- Education on signs and symptoms of PML
  - Early detection of neurological AEs allows therapy stop and neurological consult
  - Takeda proposes REMS materials and evaluations

Communicating and Managing Risk

Patient and HCP Website

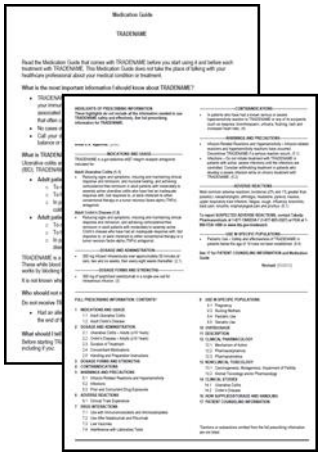


HCP Brochure



HCP and Society Letters

Label and Medication Guide



Dedicated site for all REMS materials

HCP education on PML

HCP alerts regarding safety risks and patient counseling

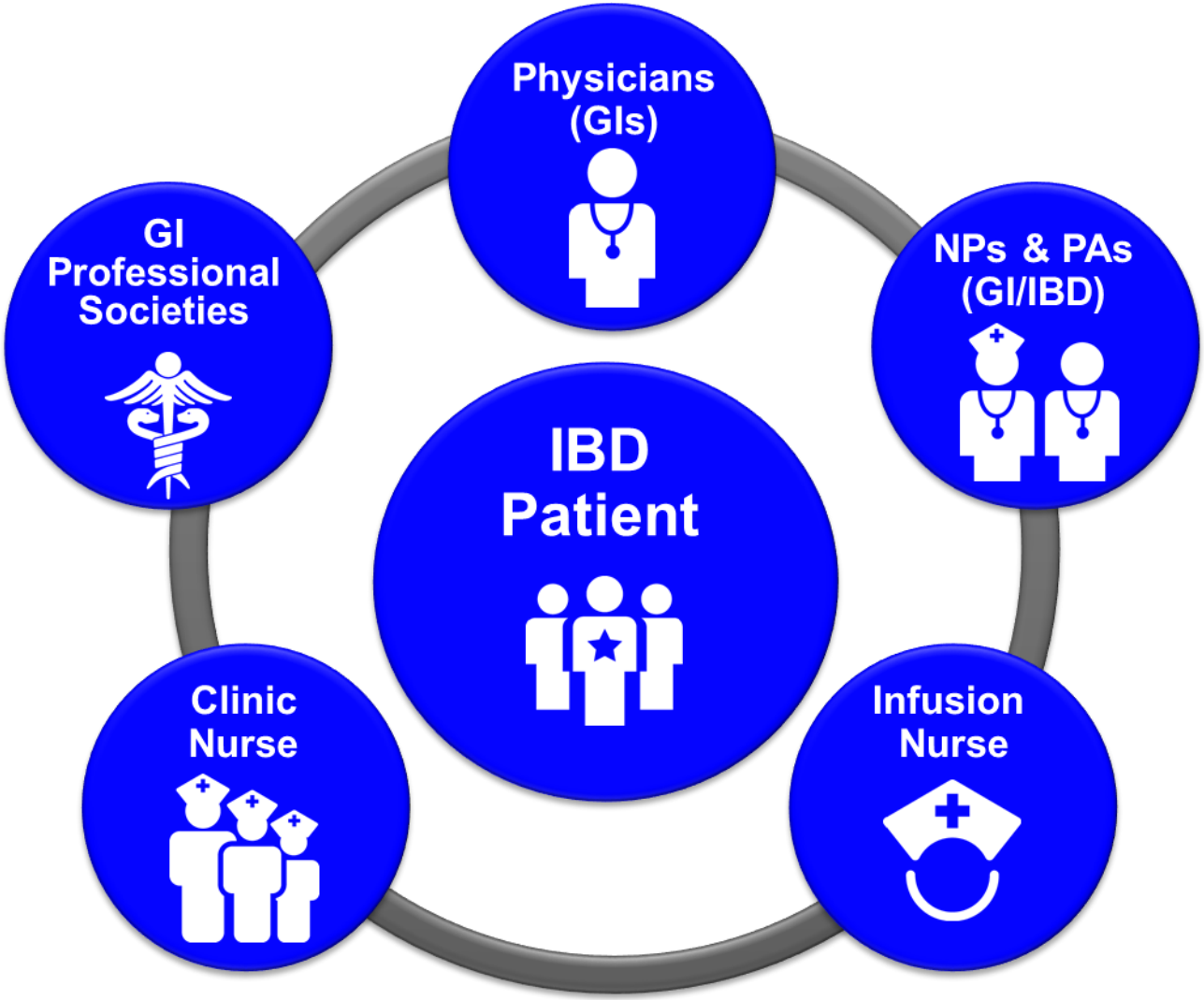
Inform patients and physicians about key safety risks & identification

Distribution methods: Direct Mail, Email, Field-Based Personnel and Online

Educational Efforts Will Assist in Reporting of Neurological Events

- Education of patients and physicians
- Defined company process for such events
- Event-specific data collection form
  - Reviewed by PML experts
- Independent review and adjudication of cases by expert committee to confirm/refute diagnosis

Targeting Multiple Stakeholders Involved in the Care of Patients with IBD



RMP Should be Proportionate to Risk and Consider Treatment Setting

- Natalizumab-like ETASU
  - Vedolizumab is different from natalizumab
  - Restrictive REMS not reflective of current risk profile
- Standard labeling and pharmacovigilance
  - Does not address education need
- Labeling, post-approval observational study and communication REMS
  - Proactive vigilance through education
  - Flexible and adaptable design

Vedolizumab Benefit-Risk in Ulcerative Colitis and Crohn's Disease

Bruce Sands, MD

Vedolizumab Benefit-Risk in IBD

- UC and Crohn's disease are impactful diseases
- Therapeutic choices in IBD are limited
- Vedolizumab offers novel mechanism of action
- IBD patients and their doctors are used to considering risks and benefits
- Durability of effect is important

Vedolizumab Benefit-Risk in IBD

- Acceptable safety profile
- Efficacy in a broad range of patients
- Induction effect of vedolizumab is important
- Maintenance effect even more impactful
- CS-sparing effect of vedolizumab (including CS-free remission) in CD and UC
- Vedolizumab would be valued as an additional option with novel MoA for durable control of IBD

Vedolizumab®

Takeda Pharmaceuticals

Joint GIDAC and DSRMAC Meeting

December 9, 2013